Status Epilepticus in the Netherlands

A Study on Causes, Therapy and Outcome

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Status Epilepticus in the Netherlands

A Study on Causes, Therapy and Outcome

Een wetenschappelijke proeve op het gebied

van de Medische Wetenschappen

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De Allerbeste keuze...

Chapter 1

Introduction and aims of the study

During my training for neurologist I treated only a few patients with status epilepticus (SE). Most responded well to therapy with benzodiazepines and/or phenytoin. It was during my first year as neurologist working in the Intensive Care Unit of the University Hospital that I came in contact with cases refractory to first line drugs and I was struck by the lack of treatment protocol, not only in our but also in the referring hospitals. The importance of a treatment protocol and the risks when such a protocol is lacking is illustrated by the following case-report.

Case report

Patient A suffered from partial epilepsy with tonic-clonic seizures caused by a severe head trauma at the age of 4 years. The prescribed anti-epileptic drugs were taken irregularly. At the age of 20 years he suffered from a generalized tonic-clonic seizure that lasted 60 minutes. He remained unconscious and from time to time showed clonic jerks. Two and a half hours after the start of the seizure his family called the general practitioner who injected 10 mg of diazepam intravenously. He was transferred to a local hospital six hours after the start of the seizure, still in coma. On admission his Glasgow Coma Scale EMV-score was 3, his blood pressure was too low to measure, his body temperature was 38.7 C°, he showed a shallow breathing pattern and was cyanotic. He was treated with intravenous (i.v.) fluids containing bicarbonate (pH was 7.29) and corticosteroids. After this treatment he reacted to pinpricks, his body temperature declined to 36.9° C and his blood pressure increased to 120/80 mm Hg. A lumbar puncture showed normal pressure. His coma, however, did not improve and the next day, as he showed asymmetrical pupils, he was transferred to the intensive care unit (ICU) of a University hospital. At admission, he was in coma, his EMV-score was 3, he showed signs of respiratory insufficiency, and his right arm was severely swollen. Laboratory investigations showed hyperkaliaemia, renal and hepatic insufficiency, hypoxia and a CPK of 150.000 U/l.

An EEG showed generalized slow wave activity, especially on the left, with every two seconds spike-wave activity with phase-opposition over the left temporal area, but sometimes also over the right. A CT-scan was normal. A muscle needle-biopsy of the right arm showed severe necrosis. Treatment consisted of intubation, mechanical ventilation, administration of clonazepam and phenytoin iv, corticosteroids iv and dialysis. However,

he died six days after the start of SE after a period of severe intracranial hypertension with pressures over 80 mm Hg. Neuropathological examination of the brain showed severe ischaemic lesions with oedema of the cerebral cortex and thalamus and to a lesser extent of the hippocampus. The pons and medulla oblongata showed only minor changes, whereas the cerebellum appeared normal. In the kidney myoglobuline was present in the renal tubulus.

This patient with partial epilepsy and compliance problems developed generalized tonic-clonic SE; due to family and doctor delay, treatment was started too late and, moreover, was also inadequate. In the local hospital, attention had been focussed on the coma. The possibility of subtle generalized tonic-clonic SE with minor clinical convulsive signs, coma and continuing epileptic discharges had not been considered. In this patient, almost all possible medical complications were present: respiratory insufficiency, hypotension, hyperthermia, renal failure, hepatic failure, rhabdomyolysis, intracranial hypertension, acidosis and hyperkaliaemia. The exact cause of death was, however, difficult to determine; the mechanisms underlying the neuropathological findings in this patient were the epileptic discharges, the medical complications or both.

In the Dutch medical literature few case reports and reviews have been published within a period of 45 years on generalized convulsive SE (Frederiks, 1969; Hootsmans, 1954; Lorentz De Haas, 1960; Verjaal and Goor, 1969; van Huffelen, 1983), absence SE (Visser, 1970), simple partial SE with aphasia as the main symptom (Jongsma and Vanneste, 1991), complex partial SE (Storm and Casteelen, 1999), the Landau-Kleffner Syndrome (Stroink *et al*, 1997) and treatment with clonazepam (van Huffelen and Magnus, 1976). The importance of a treatment protocol has been stressed in one review in the Dutch medical literature (van Huffelen, 1983).

Most cases of SE are successfully treated with first line drugs, such as benzodiazepines (BDZ) and/or phenytoin (PHT). Refractory cases of SE are relatively rare. This may be an explanation why treatment of SE lacks a consistent protocol.

This lack of a protocol is not limited to the Netherlands. In the UK little agreement about treatment of SE exists. Guidelines were absent

or inadequate in 14 different centres in the UK, in only 5 centres specific timing for drug treatment was mentioned (Martland *et al*, 1998). Also, the management of refractory generalized convulsive status epilepticus (GCSE) in three European countries by epileptologists and critical care neurologists appeared heterogenous in many aspects (Holtkamp *et al*, 2003). Finally, a prospective study in Ireland showed considerable variability in the management of convulsive SE (Najam *et al*, 2004).

Personal experience (see case-report), the lack of a consistent treatment protocol and the high percentage of poor outcome in patients with refractory SE have been the reasons to make a study of SE in the Netherlands, to make a concept of a time-scheduled protocol for the treatment of SE (Scholtes and Dries, 1986) and to promote consensus on treatment of SE.

At the start of the study the following facts were obvious:

1. No information is available on the frequency of the various types of status epilepticus in the Netherlands.
2. No information is available on causes, therapy and outcome of the various types of status epilepticus in the Netherlands.
3. There is a lack of protocol in the treatment of status epilepticus, especially in cases refractory to first line drugs in the Netherlands.

For this reason we started a retrospective study to investigate the extend of this problem in the Netherlands. After an extensive study of the literature on this topic we analysed a representative sample of cases with status epilepticus (SE) in adults and children.

With regard to outcome we looked at factors, mentioned in the literature, which may influence outcome: duration of SE, aetiology, presence of medical complications and quality of treatment. Finally, we analysed SE in special subgroups: mentally retarded patients, children with cognitive deterioration and electrical status epilepticus during slow sleep and patients admitted to the intensive care unit because of generalized convulsive SE.

The ultimate goal of this study was to provide data on outcome of SE in the Netherlands and to investigate whether these results would advocate the need to promote treatment of SE according to a time-scheduled protocol.

Chapter 2

Methods

The incidence of status epilepticus (SE) in the Netherlands is not known. SE may occur at home in a person known with previous epilepsy and recurrent periods of SE, controlled by rectal diazepam or clonazepam. This patient will not be admitted to a hospital. The same goes for patients with mental retardation and epilepsy, institutionalised in an asylum or epilepsy centre with their own care-unit. Only cases refractory to first line drugs will be transferred to a general hospital for further treatment. One of the epilepsy centres has an Intensive Care Unit of its own and internal transfers from wards of the centre to the ICU are not reported to the SIG, the Dutch documentation centre which coordinates and collects nationwide hospital statistics.

In the same vein cases of SE in patients already hospitalised because of another medical problem are difficult to trace. These secondary cases are often not mentioned in the dismissal form or instead of SE only epilepsy is mentioned.

Only admissions to hospitals are reported to the SIG. If a patient is admitted to the hospital for SE, the medical condition will be classified according to the International Classification of Diseases of the World Health Organization, ICD-9. Patients with SE receive the code 345.2, 345.3 or 345.7 and are reported to the SIG. The Central Bureau of Statistics (CBS) collects mortality figures in the Netherlands of any cause; patients who died because of SE will be reported to the CBS. For our study we asked both the SIG and the CBS how many cases of SE they recorded per year, during the period 1980 - 1987. During the period 1980 - 1985 the percentage of general and university hospitals in the Netherlands that report their diagnosis (with age and gender) to the SIG increased from 95 to 100% (SIG, 1989).

The ICD-9, however, distinguishes only three possible types of SE: petit mal status epilepticus (345.2), grand mal status epilepticus (345.3) and epilepsia partialis continua (345.7). Both petit mal SE and grand mal SE are terms no longer accepted in the classification of the International League Against Epilepsy (ILAE). A separate code for complex partial SE or tonic SE is not available. One can only guess how a case of complex partial SE has been reported: perhaps as petit mal SE or when clonic jerks have been present even as grand mal SE? It is up to the imagination of the physician how to document a case of elementary partial SE with aphasia as the sole presenting sign.

Apart from the problem that all cases of SE in a certain period are hard to trace and the limited possibilities of a proper ICD-code there is another problem: Which definition of SE has been used? Which duration of the seizure is considered to be minimal in order to diagnose SE?

Finally, some cases of SE will die before reaching the hospital or will not be admitted because they have not been recognized as such: cases of absence SE or complex partial SE may be mistaken for behaviour or psychiatric problems.

For all these reasons it is impossible to detect all cases of SE in a certain year. With these restrictions in mind, we tried to trace as many as possible admissions because of SE to a number of hospitals, in the period 1980-1987. Selection was based on size and geographical distribution. Also, cases from 2 of the 3 epilepsy centres in the Netherlands were collected.

Next we asked the SIG how many cases of SE had been reported during that same period 1980 - 1987. The figures provided by the SIG represent the number of hospital discharges and we took only notice of SE if it was the major diagnosis.

We asked the cooperation of neurologists in 50 different hospitals, spread all over the country, to supply their material about this subject. Fourteen hospitals agreed to cooperate, two of which could not be used, because adequate documentation of admissions and discharges was not present. We visited every hospital and made an on the spot investigation of the patient files. Only cases with minimum seizure duration of 30 minutes or an established succession of generalized convulsive seizures without regaining consciousness between the seizures were included. The patient was given a number to prevent any possibility of recognition and the following data were gathered: age, gender, duration of SE, type of SE, results of EEG investigations when performed, previous epilepsy or not, causes of previous epilepsy, causes of SE, precipitating factors, medical complications, therapy, admission to Intensive Care Unit, results of treatment and outcome.

Outcome has been defined for this study as the condition at discharge from the hospital, morbidity as all new neurological signs occurring because of SE and calculated per event. Outcome was good when SE had been successfully terminated and the patient returned to baseline level.

The causes of morbidity and mortality were classified as:
a) The underlying causes (cause).
b) The seizures themselves and accompanying medical complications (SE).
c) Cases in which the contribution of the underlying cause or the seizures themselves could not exactly be established (unknown).

Therapy was considered insufficient when:
a) An insufficient dose had been administered.
b) The route of administration was wrong (*e.g.* intramuscular diazepam).
c) Unnecessary delay was present (*e.g.* waiting for more than one hour after diazepam injection, while seizures continued).
d) Mechanical ventilation was not started despite signs of respiratory insufficiency or the presence of various medical complications.
e) EEG monitoring was not performed in cases treated with anti-epileptic drugs together with curarisation.

In order to find out whether the number of patients we analysed from the medical files, which were transmitted to us by the several hospitals, corresponded to the number the SIG had published, we took a sample from 5 hospitals we had visited. The SIG reported a number of 126 discharges in the period 1985 - 1987; in the corresponding period we collected 116 in the same hospitals, a 92% agreement.

Our cohort of patients in 12 hospitals and 2 epilepsy centres amounts to 576 adult cases and 112 children. In the corresponding period the average annual number of cases reported to the SIG were for generalized convulsive SE 469 (±69), for absence SE 36 (±6) and for epilepsia partialis continua 50 (±17). Our number of cases admitted because of SE can be considered representative for the situation in the Netherlands. This representative sample has been used for further analysis of causes, treatment and outcome of SE in the Netherlands.

Chapter 3

A review of the literature on status epilepticus

Generalized Convulsive Status Epilepticus. Pathophysiology and Treatment. Pharm.World Sci. 1993; 15: 17-28.

Status Epilepticus.
Scholtes FBJ. In: Vinken P, Bruyn G (Eds.), Meinardi H (Vol. Ed.). Handbook of Clinical Neurology, vol.73: The Epilepsies, part II. Amsterdam, Elsevier, 2000: 317-347.

3.1 Definition of status epilepticus

One of the earliest descriptions of status epilepticus (SE) has been found on Babylonian clay tablets, which were part of a medical diagnostic series, known as Sakikku ("All Diseases") and which date back to the period 1067 - 1046 B.C. (Kinnier Wilson and Reynolds, 1990).

Since then SE has received only little attention in the medical history. Hippocrates (fourth century BC) described several medical complications after longstanding seizures and stated that a severe fit could kill a person (Temkin, 1971). Galen (second century AD) did not mention conditions resembling SE. Caelius Aurelianus (fifth century AD) described several patients with prolonged seizures, but thought it hardly possible that this disease should assume an unremitting form (Drabkin, 1950). It was only after the start of the separate hospitalization of patients with epilepsy in the beginning of the 19th century, that systematic studies of epilepsy and SE could start. The several types of seizures were described, including SE, a term generally confined to grand mal status or état de mal: *"C'est ce que les malades l'appelent entre eux"* (Temkin, 1971). This term état de mal, coined by the patients themselves, was described for the first time by Calmeil (1824) in his dissertation. The expression SE appeared first in the translation of Trousseau's lectures on clinical medicine in 1867. SE was described as a succession of generalized convulsive seizures (Calmeil, 1824) or prolonged convulsive attacks (Turner, 1907). Other types were not acknowledged (Gastaut, 1967). According to Hunter (1960) the frequency of SE increased after the introduction of bromide by Locock in 1861. Gowers (1901) described 7 patients who died because of SE caused by sudden withdrawal of bromide. Whether this may explain why SE was so infrequently reported before that time is doubtful, because it is known that most cases of SE occur in patients without a history of previous seizures and is often caused by cerebral problems such as infections, brain tumours or stroke (CVA). The discovery of the EEG (Hans Berger, 1924) stimulated further research of SE with major consequences for therapy and classification. Important in this respect was the discovery of the EEG-correlates of petit mal status (Lennox, 1945) and psychomotor SE (Gastaut et al, 1956). The conference in 1962 in Marseille on SE (Les états de Mals Épileptiques) proposed a definition, which was approved by the International League Against Epilepsy (ILAE) in 1970:

"A condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition" (Gastaut, 1967). Another important statement at the conference was that there were as many types of SE as there were types of epileptic seizure. This definition was comparable to the description in 1903/4 by Clark and Prout: *"A typical case showed the maximal development of epilepsy, in which one paroxysm follows another so closely that the coma and the exhaustion are continuous between the seizures. It may be successive or a prolonged tonic or clonic spasm lasting one hour or more or until death."*

At the symposium in Santa Monica in 1980 (Delgado-Escueta *et al*, 1983) much attention was paid to mechanisms of brain damage and to treatment. It was stressed that the definition of SE should include a minimum duration of 30 minutes. The limit of 30 minutes was not at random; beyond this period various pathophysiologic changes occur, starting in the substantia nigra (Nevander et al, 1984; Nevander et al, 1985). These pathophysiologic changes occur mainly in generalized convulsive SE and are important with regard to outcome. It is of interest to note that in an experimental setting the critical period needed to trigger self-sustaining limbic SE by continuous hippocampal stimulation was found to be between 30 and 60 minutes (Lothman, 1990). This observation provided an experimental underpinning for the empiric clinical choice of 30 minutes as the time frame for delineating SE.

The discussion about the definition of SE has gained much attention lately. In his excellent monograph on SE, Shorvon (1994) suggested the following operational definition: *"Status epilepticus is a condition in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms, and with a highly variable pathophysiological, anatomical and aetiological basis."* Shorvon avoided the term epileptic seizure, because there are types of status in which no overt seizure occurs (e.g. nonconvulsive epileptic confusional states, subtle generalized SE, electrical status epilepticus during slow sleep, Landau-Kleffner syndrome). The minimum limit of 30 minutes, based on physiological changes, makes the definition clinically useful. He also stressed the fact that it may be difficult to measure this time limit accurately. Shorvon considered SE as a separate entity, and not simply the repetition or prolongation of seizures.

Recent pathophysiological research has made clear that important changes may occur much earlier than 30 minutes of continuous discharges (Mello, 1997). Other arguments to adjust the operational definition of SE came from clinical practice:

1. A single tonic-clonic seizure has in the majority of cases a duration of less than 2 minutes (Theodore et al, 1994).
2. Seizures in children (with new-onset seizures) with duration of more than 7 minutes do not stop spontaneously (Shinnar et al, 2001).
3. Nearly 80% of the patients treated with placebo in the pre-hospital phase still showed seizures on arrival in the hospital, suggesting that seizures with duration of more than 5-10 minutes do not stop spontaneously (Alldredge et al, 2001).

A proposal for adjustment of the operational definition has been put forward (Lowenstein, 1999): *in patients of 5 years of age or more: the minimum duration is 5 minutes or the patient has two or more tonic-clonic seizures without recovery of consciousness; in children younger than 5 years less information is present; a minimum duration of 10-15 minutes has been suggested*. Apart from the operational definition a mechanistic definition was proposed: *a condition in which there is a failure of the normal factors that serve to terminate a typical seizure.*

A prospective clinical study compared outcome in patients with prolonged seizures (10-29 minutes) to patients with SE (>30 minutes). Mortality in patients with prolonged seizures was significantly lower than in SE. Adult and elderly patients (not children) may die having prolonged seizures. Mortality increased significantly, especially in elderly, with duration. Half of the cases with prolonged seizures stopped spontaneously with seizure activity (DeLorenzo et al, 1999). This clinical study has controversial results with regard to the possible adjustment of the definition of SE: on the one hand patients may die during prolonged seizures, suggesting to adjust the time limit to 10 minutes; on the other hand mortality increased significantly in cases with duration of more than 30 minutes, suggesting to maintain the current time limit. Another important finding was that children showed no mortality in prolonged seizures, in contrast to adult and elderly patients. This is also an argument to adjust the current classification of SE, as proposed by Shorvon (1994).

The present discussion about the definition of SE has not resulted in an overall accepted adjustment; until then the current definition of SE remains: *a seizure with a minimum duration of 30 minutes; any seizure type may evolve into a SE. A succession of generalized convulsive seizures without regaining consciousness is considered SE too* (Delgado-Escueta et al, 1983). In neurological practice, however, treatment will start when the duration of the seizure exceeds 5-10 minutes.

3.2 Classification of status epilepticus

The first systematic classification of SE has been proposed in 1962 during the first ever meeting about SE in Marseille (Gastaut, 1967). Important was the hypothesis that there were as many types of SE as there were types of epileptic seizures. Three main categories of seizure type had been identified, distinguished by both clinical and EEG features: partial, subdivided into elementary and complex; generalized, subdivided into convulsive and nonconvulsive; and unilateral. SE was similarly classified.

This classification was presented at the Santa Monica conference in 1980 without important modifications (Gastaut, 1983). Apart from somato-motor SE or epilepsia partialis continua other types of elementary partial SE were mentioned such as aphasia or somato-sensory SE.

A classification based exclusively on symptoms has the advantage that it corresponds to the current semiological classification of seizures. This clinical classification offers possibilities for practical use, provided that for each type a separate code is present, which, however, is not the case. There are, however, types of status without overt seizures: e.g. subtle generalized convulsive SE and Electrical SE during Slow Sleep. Such conditions are not easily categorized into the seizure type classification. Some seizure types may occur in different clinical contexts; e.g. myoclonic SE in coma, mental retardation or in progressive myoclonic epilepsies has significant differences with respect to form, course, prognosis and treatment. Classification by clinical context gives physiological coherence to the clinical appearance, in contrast to classification by seizure type. Classification by seizure type does not offer information about aetiology or prognosis. It also needs an adaptation for particular age groups. A particular type of SE may be less

differentiated in children than in adults, and this may also be the case in patients who are mentally handicapped. Shorvon (1994) proposed a new classification based not only on seizure type, but also on age, level of cerebral maturity, pathophysiological mechanisms and clinical features (including EEG). Most reviews, however, still use the classification (or minor variants) as proposed by Gastaut (1967). This classification is easy to use, well known and more appropriate for the use of the present available ICD-coding. The revised classification is also easy to use in clinical practice and offers also information about aetiology and prognosis. An adjustment of the ICD codes is necessary, however, for appropriate documentation. Future revisions of the ILAE syndromic classification schemes will also have to address the problems of classification of SE.

A recent attempt based on the semiological seizure classification contains rather confusing new terminology (Rona et al, 2005). One may wonder whether this extensive proposal will be practical enough to be accepted in general practice.

Table 1: Classification of status epilepticus (seizure type)

1. Generalized status epilepticus	a. Generalized convulsive status epilepticus. Tonic-clonic status epilepticus. Tonic status epilepticus. Clonic status epilepticus. Myoclonic status epilepticus. b. Generalized nonconvulsive status epilepticus.
2. Unilateral status epilepticus	
3. Partial status epilepticus	a. Elementary partial status epilepticus. b. Complex partial status epilepticus.

Table 2: Revised classification of status epilepticus (Shorvon, 1994)

Status epilepticus confined to the neonatal period	1. Neonatal status epilepticus. 2. Status epilepticus in neonatal epilepsy syndromes.
Status epilepticus confined to infancy and childhood	1. Infantile spasms. 2. Febrile status epilepticus. 3. Status epilepticus in childhood myoclonic syndromes. 4. Status epilepticus in benign childhood partial epilepsy syndromes. 5. Electrical status epilepticus during slow sleep. 6. Syndrome of acquired epileptic aphasia.
Status epilepticus in childhood and adult life	1. Tonic-clonic status epilepticus. 2. Absence status epilepticus. 3. Epilepsia partialis continua. 4. Myoclonic status epilepticus in coma. 5. Specific forms of status epilepticus in mental retardation. 6. Myoclonic status epilepticus in other epilepsy syndromes. 7. Nonconvulsive simple partial status epilepticus. 8. Complex partial status epilepticus. 9. Boundary syndromes.
Status epilepticus confined to adult life	1. De novo absence status epilepticus of late onset.

3.3 Epidemiology of status epilepticus

3.3.1 Case-ascertainment

Several studies have attempted to quantify the frequency of SE in various clinical populations. These surveys were until recently retrospective with all their inherent inaccuracies. Apart from the retrospective nature of most studies there are several other potential problems one should consider:

a. The diagnosis of SE in clinical practice is not always easy. When one observes a seizure, this may be a single seizure or part of serial seizures or part of SE. The post-ictal clinical presentation may offer problems too: has the seizure stopped entirely (an EEG is not always available), will another seizure start?
b. The diagnosis is not always considered, especially non-convulsive SE in mentally retarded patients or patients with confusion, mistaken for a psychiatric diagnosis.
c. A number of cases will not reach a hospital; they are treated outside neurological services. This is e.g. the case in patients known with epilepsy and mental retardation, living in an asylum. When they develop SE, they will be treated locally and only admitted to a hospital when SE is refractory to first line drugs.
d. SE in patients already admitted because of another medical problem will not always be documented as such.
e. Duration of seizures will not always be recorded; short status episodes may be categorized as seizures, not as SE.
f. In clinical practice therapy is not awaited for, but is instituted especially when an acute exacerbation is present in a patient known with previous epilepsy, or when serial seizures are present. An incorrect dismissal diagnosis of SE is not rare in these cases.

Recent prospective studies have mentioned the problem of under-ascertainment (DeLorenzo et al, 1995; Knake et al, 2001). Studies like these must adhere to the rigid definition of SE; probable cases must be excluded. This is e.g. the case in patients controlled in 10-30 minutes, which, most likely, were cases of SE. The studies in Virginia (DeLorenzo et al, 1995) and in Germany (Knake et al, 2001) calculated a rate of under-ascertainment in the area outside the primary service area of the investigating hospital of 67% respectively 73,6%. Many cases of SE will not be brought to the attention of the adult and paediatric neurological staff and remain unidentified.

Several other studies underline this problem of case-ascertainment:

– In patients with epilepsy attending a university hospital the diagnosis was false negative (CVA, confused, tremor, other) in 25 of 32 cases and false positive (subdural hematoma, partial seizure, tumour) in four: the role of the neurologist was important for a correct diagnosis (Berger et al, 1999).

– A 24-hour-status-epilepticus-team confirmed the diagnosis of generalized convulsive SE in 57 of 77 cases, but not in the other 20 patients. In 29 cases with movements suggesting SE, in only 8 patients the diagnosis of SE was confirmed; in 21 patients another diagnosis was present (Handforth et al, 1993).
– A comparable result was mentioned by Garnett et al (1994): the regular staff did not recognize SE in 13%, this was corrected by the status-epilepticus-team.

3.3.2 Incidence and prevalence

The annual number of admissions because of SE has been estimated as 1-8% of all hospital admissions for epilepsy (Hauser, 1990). Several studies concerning adult patients and/or children have confirmed this for both university hospitals and general hospitals (Pilke et al, 1984; Krumholz et al, 1989; Smith et al, 1996; Berger et al, 1999; Reuber et al, 2000). A retrospective chart review of patients presented to 12 emergency departments showed that 6% of the patients with seizure-related presentations (= 1,2% of the total patient group) were in SE (Huff et al, 2001).

SE may be the presenting symptom of epilepsy (initial SE), occurring during the course of epilepsy (intercurrent) but also in cases without any history of epilepsy (isolated). In children SE is often the first epileptic event, reflecting the high incidence of acute aetiologies and febrile status (Aicardi and Chevrie, 1970; Phillips and Shanahan, 1989). In the elderly, after the age of 60, SE is also often the initial epileptic manifestation, with a high percentage of focal structural cerebral pathology. In a prospective study of 204 patients with a single unprovoked seizure (10% < 16yrs) 18 cases showed SE as the first seizure (9%). SE was not a risk factor for recurrence of seizures (Hauser et al, 1998).

Important factors that may influence the frequency of SE are age, the presence of a mental handicap, the presence of symptomatic epilepsy and frontal lobe pathology (Shorvon, 1994).

The number of cases with SE shows a slight peak at less than one year and gradually declines until early adulthood. Thereafter the number of cases increases as the population ages (DeLorenzo et al, 1996). The prospective

study in Virginia found an incidence of 41 per 100.000 inhabitants; the incidence in children with an age of less than 1 year was 150 per 100.000, in the elderly (>60 years) 60 per 100.000 (DeLorenzo et al, 1996). The retrospective study in Rochester mentioned an incidence of 18 per 100.000; in children (< 1 year) 135 and in the elderly 62,5 per 100.000 (Hesdorffer et al, 1998). Of all the children with SE 40% is less than 2 years of age (Shinnar et al, 1997).

The proportion of patients with SE who are known with previous epilepsy depends on age and the cause of epilepsy. In idiopathic epilepsy this number is 1,6%, in symptomatic epilepsy 9% (Janz, 1961). Between 0.5-1% of patients with established epilepsy will experience at least one episode of SE annually; within 5 years of initial diagnosis of epilepsy, 20% of patients will experience an episode of SE (Hauser, 1990). The incidence of SE in patients with established epilepsy in adults is lower than in children. Literature before 1980 mentioned 5-10% occurrence of SE in adult patients with previous epilepsy (Turner, 1907; Lennox, 1960; Janz, 1961); in children the occurrence was 10-20% (Aicardie and Chevrie, 1970; Yager et al, 1988). In a long-term follow-up study during 30 years in 245 children with active epilepsy, 78 showed SE (32%). In 20 children SE was initial, 44 cases had recurrent SE. Remote symptomatic epilepsy was present in 44% of the children with SE, idiopathic/cryptogenic in 20% (Sillanpää et al, 1998). In recent population-based studies SE was present in 10% (Berg et al, 2004) to 27% (Sillanpää and Shinnar, 2002) of the children with epilepsy. The occurrence of SE in these children did not influence mortality or remission of epilepsy (Sillanpää and Shinnar, 2002). The incidence of SE in 3 cohorts of patients with complex partial seizures, not in remission, was for all types of SE in children 9-11% and in all age groups 9%. A history of SE was present in 33-38% of the children and in 27% of the group with all ages (Shinnar et al, 2001). In cases with intractable epilepsy, SE occurs more often, 44%, in patients with clustering of seizures, than without clustering, 12,5% (Haut et al, 1999).

A retrospective study by means of interviews in 598 patients with epilepsy mentioned a lifetime prevalence of SE (generalized convulsive more frequently than nonconvulsive) of 17%. The debut of epilepsy in cases with SE is earlier (Schwaner and Fountain, 2000).

Recurrence of SE occurs in adults in 13% and in children in 38%, especially in children younger than 5 years, with neurological abnormalities and decreased serum levels of anti-epileptic drugs (DeLorenzo et al, 1993). The recurrence rate of SE in children is related to the cause of SE: in febrile and idiopathic cases the recurrence rate is 3-4%, in acute symptomatic cases 11%, in remote symptomatic cases 44% and in progressive neurological disorders 67% (Shinnar et al, 1992).

According to Shorvon (1994) the risk of SE in patients with epilepsy and mental retardation is high. Little information about prevalence and incidence of SE in patients with mental retardation is available, however. Some studies mentioned the prevalence of SE in mental retardation. In a group of 98 children of 6-12 years with epilepsy and mental retardation SE occurred in 37 (37%); recurrence rate was 35% (Steffenburg et al, 1996). In a population of children and adults with mental retardation the prevalence of convulsive SE was 18,7% (Forsgren et al, 1990). These figures are not very different from those in the total population with epilepsy (Hauser, 1990). It should be noted, however, that many cases of SE in patients with mental retardation would not be documented. This is especially the case for non-convulsive SE, a diagnosis easily overlooked in patients with mental retardation.

In the period before modern imaging frontal lobe pathology was often mentioned in patients with SE (Whitty and Taylor, 1949; Oxbury and Whitty, 1971; Janz 1964). Pathological examinations in 91 patients with SE showed frontal damage in 77 patients (Peiffer, 1963). Apart from Aminoff and Simon (1980) more recent reviews did not mention an excess of frontal lobe pathology in SE (DeLorenzo et al 1992; Barry and Hauser 1993; Treiman 1993).

A genetic predisposition to SE has been suggested by twin studies: the risk of SE in the monozygotic co-twin of an affected individual was 90x higher in comparison to the dizygotic co-twin (Corey et al, 1998; Corey et al, 2004).

Recent epidemiological studies

Until recently little was known about the incidence of SE in the general population. Some information was published from hospital records, reviewed retrospectively. Both Hauser (1990) and Shorvon (1994) calculated the annual incidence of SE in various groups of patients and of various types of SE. The first prospective study was performed in Virginia (DeLorenzo et al, 1996). Two more prospective studies have appeared since then (Coeytaux et al, 2000; Knake et al, 2001), and one adequate retrospective (Hesdorffer et al, 1998).

DeLorenzo et al (1996) found an incidence of 41 per 100.000 individuals per year, exclusive neonates < 1 month; white 20, non-white 57. The incidence in young children, less than 1 year, and in the elderly, older than 60 years, were significantly higher: 150 respectively 86 per 100.000. Cases from community hospitals were underreported (33%). Based on the frequency of the various major seizure types and the total incidence one can calculate the incidence of the different types of SE (table 5). Mortality (table 3) in cases of <1year was 13,2%, morbidity 9,4% (Morton et al, 1998). Mortality was related to the cause of SE: in adults death-rate in anoxia was 72%, in hypoxia 51%, in CVA 33%, in metabolic causes 30%, in alcohol 20%, in remote symptomatic causes 14% (especially by CVA) and in low anti-epileptic drug levels 4%. Mortality in idiopathic cases (3% of the causes) was 25%. In children mortality occurred only in cases caused by infections (5%).

Another study in the USA has been performed in Rochester (Hesdorffer et al, 1998). This population-based study was retrospective; it was not reported whether neonates (age < 1 month) were excluded or not .The age-adjusted incidence of SE was 18,3 per 100.000. The incidence increased from 13,9 during the period 1965 - 1974 to 22,4 in the period 1974 - 1984. The increase was due to an increased incidence of acute symptomatic SE due to anoxic encephalopathy in the elderly. The difference in incidence with the study in Richmond (DeLorenzo et al, 1996) was partly explained by the larger non-white group in Richmond (57% versus 4%). The incidence in the male population was twice the female.

Excluding febrile SE (16 cases), SE was generalized without focality in 28% of the cases, secondary generalized in 17%, and partial only in 41%. Absence and myoclonic SE were less common: 3 and 10%. Complex partial SE was not mentioned separately.

Incidence rates per 100.000 for the various seizure types of SE (excluding febrile status) can thus be calculated: generalized SE 8,2; partial 7,5; absence 0,6 and myoclonic 1,8. A second episode of SE occurred in 36 cases (18%), especially in acute symptomatic causes (15 cases). Previous epilepsy was present in 46% of the cases. Duration was <24hrs in 75%; 38% lasted less than 2 hours. The risk of SE of longer duration was greatest in children less than 1 year and in the elderly. The cumulative incidence at 60 years of age was 2 per 1000 and at age 85 years 5,7 per 1000; an increase of 62% was noted between 60 and 75 years and of 44% between 75 and 85 years.

A population-based study of SE in the French-speaking part of Switzerland found a crude incidence of 9,9/100000 and an age-adjusted of 10,3/100000 (Jallon et al, 1999; Coeytaux et al, 2000). Cases with post-anoxic encephalopathies were excluded. The incidence was highest in the area of Geneva (16,3), which could be explained by perfect ascertainment of the cases. In this area EEG monitoring was possible 24 hours a day and 7 days a week. This prevented under-diagnosis of cases with non-convulsive SE. Incidence of SE outside the canton of Geneva was 7-10/100000. Taken into account the exclusion of post-anoxic cases in this study, one may conclude that the incidence in the area of Geneva corresponds to the incidence in Rochester and to the incidence in the white population in Virginia. The male/female ratio was 1.47. The age-specific incidence rates showed the same bimodal distribution as in Rochester and Virginia. The lower rate in the elderly in this study could be attributable to the exclusion of post-anoxic cases. The cumulative incidence at age 85 years was 2,5 per 1000. The incidence in children less than 1 year was not mentioned. Incidence is children less than 4 years was 38.7/100000, in children (0-14 years) 20,6/100000, in adults (15-59 years) 5,2/100000, and in the elderly (> 60 years) 15,3/100000.

The most frequent initial seizure type was partial (44,8%). About one-third of these evolved to secondary generalized SE. Primary generalized tonic-clonic SE was present in 33,1%, simple partial in 18,1% and complex

partial in 26,7%. Other seizure types included absence, tonic and hemi-convulsive (in children only). Duration of SE was less than 24 hours in 66,7%. A previous period of SE was present in 48% of the cases with previous epilepsy.

Total mortality was 7,6%; in the canton of Geneva mortality was 6,6%. The exclusion of post-anoxic cases and the prompt management starting before admittance to the hospital may explain the low mortality rate in this study. In 58,7% therapy started during transport to the hospital.

A recent prospective population-based study of SE in Germany was restricted to adult patients (Knake et al, 2001). The crude average incidence rate per 100.000 in the primary service area was 15,8 and the age-adjusted incidence 17,1. The incidence in the elderly was 54,5 and 4,2 in the group of 18-59 years. It was higher in the male (26,1) than in the female population (13,7). The crude average incidence rate in the area outside the primary service area was only 4.5. This suggested a rate of under-ascertainment of 73,6%; this corresponds to the rate in community hospitals in Virginia of 67% (DeLorenzo et al, 1996). The incidence rate in the primary service area in this study (17,1) corresponds to the retrospective rate in Rochester (17,4 in adults older than 20 years). A comparison with the studies in Virginia and Switzerland is difficult because these studies included children. Seizure type was mainly partial (76%), with (19,3%) or without secondary generalisation (57%). Duration varied from 0,5-430 hours, with a mean of 18,6 hours. Previous epilepsy in the primary service area was present in 33%, outside this area in 55,9%. The causes of SE were remote or acute symptomatic in most cases (74%). Mortality rate (< 30 days) was 9,3%. The age of those who died was not mentioned.

A comparable incidence rate of GCSE to the studies in Rochester, Switzerland and Germany (table 5) has been found in California (Wu et al, 2002). The case fatality was 10,7%; this was considerable lower than in Virginia, but not very different from Germany and Switzerland.

A study in Bologna, Italy, found an incidence of 13,1 per 100.000 for patients older than 20 years, including cases with onset inside the hospital (Vignatelly et al, 2003). This study mentioned a high 30-day case fatality of 39%, which was explained by inaccurate patient management.

3.3.3 Conclusions

The recent population-based epidemiological studies of SE suggest an annual incidence of SE of 18-41 per 100.000 (table 5 and 6). The incidence in the male population is twice the female. Previous epilepsy is present in about 40% of the patients. Duration of SE is in most cases less than 24 hours. The cause is acute symptomatic in more than 50-60% of the cases. The most frequent seizure type is generalized convulsive, especially secondary generalized, and partial; absence and myoclonic SE are relatively rare. The incidence of SE, based on the population-based studies, should de estimated on 20 per 100.000 at the least (Chin et al, 2004). One may expect at least 3000 new cases of SE in the Netherlands (16 million inhabitants); the results in Virginia and the calculations of Shorvon (1994) indicate an even higher incidence: 6500-10000. The associated number of deaths is hard to define; extrapolating the findings of Virginia, this number may vary between 660 and 1430 annually in the Netherlands. The results in Switzerland are exclusive the post-anoxic group, which in most cases have a bad outcome. The study in Germany was restricted to adult patients. When one extrapolates the findings in Germany to the Netherlands (about 12 million people older than 17 years), the annual number of cases with SE in the age group older than 17 years will be about 2052; the annual number of associated deaths about 190.

Table 3: Some characteristics of status epilepticus in the Richmond study*

	Previous epilepsy (%)	Recurrence rate (%)	Mortality (%)
Children	38	35	2,5
Adult patients	54	7	14
Elderly patients	30	10	38
Total population	42	13	22

* (DeLorenzo et al, 1996)

Table 4: The incidence of status epilepticus per 100.000 individuals by age and aetiology*

Age (incidence)	Acute symptomatic	Idiopathic/ cryptogenic	Remote symptomatic	Febrile
< 1 (135)	87	5	19	24
1 – 4 (35)	11	5	5	15
5 – 9 (12)	6	3	3	0
10 – 14 (3,7)	0	1	2	0
15 – 60 (5,5)	19	7	9	0
> 60 (62,5)	114	26	44	0

* (Hesdorffer et al, 1998)

Table 5: Incidence of status epilepticus per 100.000 individuals in prospective studies, per seizure type

	DeLorenzo et al (1996)	Coeytaux et al (2000)		Knake et al (2001)
		Total	Geneva	
Total incidence	41	10,3	16,3	17,1
Tonic Clonic	29,1	3,4	5,4	5,3
Simple Partial	9,4	1,9	3,0	2,1
Complex Partial	1,2	2,8	4,4	6,9
Tonic		0,2	0,4	
Absence	0,4	0,4	0,6	1,0

Table 6: Incidence of Status Epilepticus

	Per million
Shorvon, 1994 (calculation)	441-646
Delorenzo, 1996 (prospective)	410 (excl. neonates)
Hesdorffer, 1998 (retrospective)	183
Coeytaux, 2000 (prospective)	103-163 (excl. post-anoxic)
Knake, 2001 (prospective)	171 (age >17)

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3.4 Neurophysiology and neuropathology of Status Epilepticus

3.4.1 Introduction

The neurophysiological processes that initiate status are, by common agreement, similar to those producing isolated seizures (Shorvon, 1994). The sudden cessation of epileptic activity at the termination of an ordinary epileptic seizure is, however, absent during status epilepticus (SE). Failure of cessation of seizure activity may be caused by changes in GABA-receptors, by changes in the Na-K-ATPase system, by membrane defects with abnormalities in ion-movements or by other impairments of GABA-ergic function.

Many neurochemical studies of epilepsy and SE have been focussed on the actions of GABA, the major inhibitory cerebral neurotransmitter, and of glutamate, the major excitatory amino acid. Other cerebral neurotransmitters that may be involved in SE are acethylcholine and aspartate (excitatory), dopamine, noradrenaline, adrenaline, serotonine, taurine, glycine and opioids (all inhibitory). Abnormalities have been found with almost all neurotransmitters that have been studied.

Gamma amino butyric acid (GABA) is an important inhibitory neurotransmitter, which has shown to increase the threshold for seizures, and to inhibit seizure spread. GABA-mimetics (vigabatrin) have shown to be anticonvulsant. But paradoxal findings have been mentioned too, which may be due to variations in regional susceptibility to GABA or to differences in the mechanism of focal and generalized seizures (Lortie et al, 1993). GABA is released from GABAergic neurons and binds to several types of GABA receptors: GABA-A, GABA-B and GABA-C. GABA-A receptors mediate the majority of fast inhibition in the central nervous system. During SE GABA-inhibition decreases; in the hippocampus reduced GABA-A mediated inhibition has been found, which may contribute to the self-sustaining nature of the epileptic discharges during SE (MacDonald and Kapur, 1999). The pharmacological properties of GABA-A receptors have been shown to depend on subunit-subtype composition. There are 5 subunits with a varying number of subtypes. The composition of the GABA-A receptors is determined by genetical properties. The properties of the GABA-A receptors

include formation of a chloride channel, enhanced by barbiturates and diazepam. Benzodiazepine sensitivity requires the presence of a γ-subunit, the subunit location of the barbiturate-binding site is unknown. During treatment of SE in rats, diazepam, but not phenobarbitone, showed a rapid loss of efficacy, because of rapid modification of the functional properties of GABA-A receptors during SE (MacDonald and Kapur, 1999).

This is in agreement with results in human clinical studies.

The most important excitatory neurotransmitter is glutamate, whose actions are complex. Several subtypes of glutamate receptors have been demonstrated: N-methyl-D-aspartate (NMDA), kainate, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and several metabotropic receptors (Meldrum, 1994). Apart from anticonvulsant activities, glutamate receptor antagonists have also shown to inhibit neuronal damage in experimentally induced SE (Clifford et al, 1990; Bertram and Lothman, 1990). The role of glutamate in neuronal damage during SE will be discussed in the chapter on neuropathology.

3.4.2 Neurophysiological changes during generalized convulsive SE

Most of the studies on physiological changes in SE concerns generalized convulsive SE and in particular tonic-clonic SE (TCSE). The physiological changes during TCSE may be the result of the neuronal discharges, affecting the hypothalamus and brainstem centres, and/or the secondary effects of increased motor activity on the blood circulation. The increased demand by the cerebral tissue for oxygen because of the continuous seizures, causes an increase of cerebral blood flow (CBF) of 200-600%, mediated by the increase of systemic blood pressure and a decrease of cerebro-vascular resistance. The increase of CBF shows regional differences (Horton et al, 1980).

A prompt increase in epinephrine and norepinephrine plasma levels contribute to peripheral vasoconstriction, the rise of systemic blood pressure and the occurrence of cardiac arrhythmias. ECG investigation during and after SE shows a high percentage of abnormalities, such as axis-changes, conduction abnormalities, ischaemic patterns or arrhythmias. These changes may be responsible for myocardial dysfunction or ischaemia and may occur during but also after SE. ECG monitoring is necessary until 24-48 hrs after the SE has been arrested (Boggs et al, 1993).

During the first 30 minutes of SE a prompt fall of blood pH occurs because of lactate production, inducing motor paralysis can markedly attenuate this.

Cerebral metabolic rate for oxygen (CMR-O) and glucose (CMR-gluc) are increased, especially in known vulnerable regions; cerebral energy state remains stable. With ongoing seizure activity, however, the cerebral energy state declines after 60-90 minutes of TCSE. Important in this respect is the decline of cerebral auto-regulation after 30 minutes. Cerebral perfusion pressure becomes dependent on systemic blood pressure. After 40-50 minutes of SE blood pressure starts to fall, despite ongoing seizures and very high levels of plasma catecholamin-concentrations. Deterioration of vascular reactivity in ongoing SE results in decreased ability to deliver oxygen to focal areas of metabolically hyperactive cerebral tissue. These episodes of local transient hypoxia may contribute to neuronal damage (Kreisman et al, 1983). Other medical complications become apparent too: respiratory depression, hyperthermia, decrease of systemic and cerebral glucose levels with ongoing increased CMR-gluc, excessive sweating, increased salivary and bronchial secretion, pulmonary edema, disseminated intravascular coagulation and hepatic failure. Metabolic problems include hyponatraemia and hyperkalaemia. Hormonal changes other than the increase of epinephrine and norepinephrine include an increase of cortisol (Calabrese et al, 1993). Prolactin levels do not change significantly (Lindbom et al, 1993). Insulin and glucagon levels rise because of stimulation of autonomic neurons. The increased levels of epinephrine and norepinephrine also cause glucogenolysis. The net result in the early phase of SE is hyperglycaemia, but during prolonged seizures, hyperinsulinemia causes hypoglycaemia (Wasterlain et al, 1993).

Excessive motor activity and local trauma due to pressure in a comatose patient may cause rhabdomyolysis with increase of creatine phosphokinase (CPK), tubular necrosis because of accumulation of myoglobin and renal failure. Intracranial hypertension is caused by the increase of CBF, the loss of autoregulation, the decrease of pH (vasodilatation), oedema and the discharges themselves (Gabor et al, 1984). Leucocytosis is frequent, even in the absence of an infection. Investigation of cerebral spinal fluid may show pleiocytosis and increased protein content. Pleiocytosis during SE is especially determined by the underlying cause; in cases in which the causal factor is usually associated with normal CSF, the number of cells was low (Barry and Hauser, 1994).

Vomiting, urinary or bowel dysfunction, inhalation and asphyxia because of secretions or vomit, loss of weight, trophic abnormalities and bedsores may be present.

It is obvious that these medical complications may contribute to neuronal damage and should be adequately treated (Meldrum, 1983; Glaser, 1983; Simon, 1985; Lothman, 1990; Brown and Hussain, 1991; Shorvon, 1994).

The physiological stages in TCSE may be divided into two phases: phase I is the early (compensated) stage and phase II the late (decompensated) stage. The shift from phase I to phase II usually occurs after 30 minutes, although great variation is seen in clinical practice, depending on aetiology, the location and severity of the seizures and the instituted therapy. The decline of cerebral auto-regulation after 30 minutes is of importance with respect to the shift of phase I to phase II. The various physiological changes during TCSE are mentioned in table 7 (phase I) and table 8 (phase II).

In an experimental setting it was found that hyperthermia in rats caused an increase of the level of glutamate with corresponding decrease in seizure threshold (Morimoto et al, 1993). Lowering of body-temperature to 28°C caused a decrease by 50% of the ictal discharges in rats with SE caused by kainic acid. Hippocampal cell loss was observed in all rats with SE and normal body temperature, but in none with a temperature of 28°C. Hyperthermia caused an aggravation of seizures and of brain damage (Liu et al, 1993). In earlier experiments the role of hyperthermia with regard to cerebellar damage had been established (Meldrum and Brierley, 1973). In ventilated and paralysed animals, not only hyperthermia is less severe, but also hypotension and acidosis, with less cardiac arrhythmias. However, control of various parameters, such as blood pressure, pO_2, pH, pCO_2 and temperature, does not prevent neuronal damage in ongoing SE. Despite these optimal circumstances, neuronal damage may occur after 30 min. in the substantia nigra pars reticularis, after 45-60 min. in the third and fourth layer of the cerebral cortex and in special areas CA_1 and CA_4 of the hippocampus (Nevander et al, 1984; Nevander et al, 1985; Meldrum, 1983; Siesjo and Wieloch, 1986). This selective vulnerability may be determined (among others) by the abundant number of NMDA-receptors of vulnerable neurons in these areas (Wasterlain et al, 1993). During experiments with controlled respiration, bloodpressure, temperature and treated acidosis

gross energy failure is not present, therefore the neuronal damage may be caused by the hyperexcitation. An exception is the cell necrosis in the substantia nigra (pars reticularis), which is probably caused by excessive energy failure and massive accumulation of lactate (Siesjo et al, 1986).

The reduction of GABA synthesis in the substantia nigra pars reticularis during SE in rats may be of importance with regard to seizure spread and maintenance (Wasterlain et al, 1993).

These observations in animal models suggest that patients with ongoing generalized convulsive SE should be intubated, mechanically ventilated and paralysed. Several studies about the incidence of morbidity and mortality in humans suggest that these procedures should at least start 1 hr after onset of SE (Aminoff and Simon, 1980; DeLorenzo et al, 1992). Hyperthermia and hypotension are less severe then and muscle necrosis is prevented, the possibility of renal failure and cardiac arrhythmias is decreased. Rapid termination of SE and adequate treatment of the medical complications will contribute to improved outcome of patients with TCSE.

Table 7: Physiological changes in phase I of TCSE*

Cerebral changes	Metabolic changes	Autonomic and cardiovascular changes
• Increased blood flow. • Increased metabolism. • Increased lactate concentration. • Increased glucose concentration. • No mismatch between energy requirement and oxygen/glucose supply.	• Hyperglycaemia. • Lactic acidosis.	• Hypertension. • Increased cardiac output. • Increased central venous pressure. • Massive release catecholamines • Tachycardia, cardiac arrhytmia. • Salivation, vomiting, incontinence. • Hyperpyrexia.

* (Shorvon, 1994)

Table 8: Physiological changes in phase II of TCSE*

Cerebral changes	Metabolic changes	Autonomic and cardiovascular changes
• Failure of cerebral autoregulation. • Hypoxia. • Hypoglycaemia. • Falling lactate concentrations. • Falling energy state. • Increase of intracranial pressure, cerebral edema.	• Hypoglycaemia. • Hyponatraemia. • Hyperkalaemia. • Metabolic/respiratory acidosis. • Hepatic and renal dysfunction. • Rhabdomyolysis, myoglobulinuria. • Multi-organ failure. • Leucocytosis.	• Systemic hypoxia. • Falling bloodpressure. • Falling cardiac output. • Respiratory and cardiac impairment. • Hyperpyrexia.

* (Shorvon, 1994)

3.4.3 Neuropathology in Generalized Convulsive Status Epilepticus

Experimental results in animals have shown that generalized convulsive SE may cause neuronal damage, despite optimal treatment of respiratory insufficiency, hyperthermia, hypotension and other medical complications. The ongoing discharges themselves appear responsible for neuronal damage in particular vulnerable regions of the brain: the hippocampus (especially CA_1 region), the neocortex (layer 3 and 4), the thalamus and the cerebellum (Meldrum and Brierley, 1973; Meldrum et al, 1974; Meldrum, 1983; Nevander et al, 1984; Nevander et al, 1985; Siesjo and Wieloch, 1986; Lothman, 1990). Not only generalized convulsive SE, but also complex partial SE may cause selective damage too, especially in the CA_1 and hilar region of the hippocampus and the thalamus (Lothman, 1990; Meldrum, 1993; Ben-Ari, 1997).

The cellular damage induced by glutamate is possibly related to high intracellular calcium concentrations. The increased amount of extra-cellular potassium during ongoing seizure activity causes an increased release of glutamate. Stimulation of the N-methyl-D-aspartate receptor by glutamate causes an increase of intracellular calcium and intracellular edema, mediated by excess of sodium chloride and water. When this exceeds the capacity

of the neuron to sequester or transport calcium, mitochondria take up calcium, which ultimately leads to irreversible mitochondrial damage; cell metabolism will be disturbed. Calcium overload leads to an increase in the activity of various proteases, phospholipases and endonucleases. Lipolysis and proteolysis will follow, which will result in membrane damage, receptor dysfunction and cell necrosis (Meldrum, 1983; Siesjo and Wieloch, 1986; Siesjo, 1989; Clark, 1989; Lipton and Rosenberg, 1994). The possibilities of preventing neuronal damage by excess calcium are under investigation. This concerns the role of calcium entry blockers, such as nimodipine and NMDA receptor antagonists such as MK-801, ketamine and CPP in the treatment of generalized convulsive SE (Clifford et al, 1990; Bertram and Lothman, 1990; Prasad et al, 2002). Glutamate receptor-mediated neurotoxicity in humans has been demonstrated after domoic acid intoxication (Teitelbaum et al, 1990; Cendes et al, 1995). Other mechanisms which may also be involved in the pathogenesis of epileptic brain damage are: free-radical release, the activation of synaptic phospholipases, such as phospholipase A2 (Bazan, 1997), the activation of immediate early genes by epileptic activity (Dragunow, 1997); seizures activate many other genes, such as genes coding for growth factors, but also reduction of Glutamate-R-B gene reduction has been found, which causes enhancement of calcium influx in CA3 region of the hippocampus (Ben-Ari, 1997), the breakdown of membrane phospholipids, which gives rise to a massive increase of arachidonic acid and other free fatty acids.

Experimental results in animals show that neuronal damage becomes especially evident after a recovery period of several days (Nevander et al, 1984; Nevander et al, 1985). Neuronal damage after generalized convulsive SE in animals has not been found in animals killed immediately after (Brown et al, 1980) or 1-2 hrs after (Atillo et al, 1983) generalized convulsive SE. The cascade of events from intracellular calcium accumulation to membrane damage and cell death takes time.

Status induced cerebral damage may lead to chronic epilepsy in primates, rodents and cats (Lothman and Bertram, 1993; Sloviter, 1999; Coulter, 1999). In clinical (human) studies this is hard to prove because of the confounding factor of underlying cause. Apart from selective neuronal loss as a result of SE, other contributing factors to the development of spontaneous recurrent seizures are sprouting (reactive synaptogenesis) of

mossy fibers in the dentate gyrus and altered properties of GABA receptors of surviving neurons.
The immature brain is more prone to the development of seizures, which propagate to distant sites rather readily and may last for longer periods of time. The increased excitatory drive of the immature brain is necessary for normal brain development (enhanced learning, synaptogenesis, neuronal plasticity). The overshoot in expression of functional glutamate receptors is likely to play a major role in the increased excitability of the brain in the early postnatal development. The functional GABA-ergic inhibition shows a delayed onset; GABA-A activation in the early postnatal period causes depolarisation rather than hyperpolarisation. Neurotransmitters that are inhibitory in the mature brain are excitatory in the developing brain. Because of delayed glial development extracellular potassium may accumulate and contribute to the hyperexcitable state. Other possible contributing factors are a lower level of cerebral norepinephrine, age related differences in the nigral GABA-sensitive system and the high level of CRH (corticotropin-releasing hormone)-receptors (Moshe et al, 1991; Moshe, 1993; Mizrahi, 1999; Sanchez and Jensen, 2001).

The immature brain is more prone to seizures, but less vulnerable to the longterm effects of prolonged seizures; protection of the developing brain from seizure induced damage is, however, not absolute. Apart from acute neuronal damage, seizures can induce long-lasting, potentially adverse functional changes in the immature brain that may not appear acutely as injury (Sanchez and Jensen, 2001). The incidence of seizures in the neonate is very high (1,8-5,1 per 1000 live births). It is estimated that about 33% of the neonates with seizures show SE. Outcome in neonates is especially determined by the aetiology (Mizrahi, 1999).

The results of investigations of the human brain are less conclusive than the results of animal experiments. Not in all cases of prolonged generalized convulsive SE neuronal damage has been found, albeit that in patients with epilepsy who did not have a period of SE elective necrosis may be present (Meencke and Veith, 1997). One should consider the following factors in this respect:

- SE may result from, but can also cause pathological changes.
- The use of different definitions of SE.
- The treatment employed.

– The results of secondary systemic effects of SE.
– The influence of associated pathology in the individual case.

An example of the dispute about the relation between seizures and neuronal damage is the discussion about the significance of mesial temporal sclerosis (MTS) with respect to febrile convulsions (FC): is MTS cause or consequence of seizure activity?

Already in 1825 Bouchet and Cazauvieilh mentioned a small indurated hippocampus in half of a group of 18 chronic epileptics. More than a century later Falconer suggested that severe febrile convulsions (FC) caused unilateral MTS followed by epilepsy (Falconer, 1974). A significant lower number of neurons were found in the hippocampus of patients who as a child had shown severe convulsions, especially before the age of three. A relation was present between the degree of neuronal loss and a duration of more than 30 minutes, a restriction to one side of the body or when followed by a transient weakness on one side (Sager and Oxbury, 1987). Other studies support Falconer's suggestion that prolonged childhood FC may cause MTS, which is the cause of partial epilepsy in later years (Kuks et al, 1993; Cendes et al, 1993). The relation between prolonged duration of FC in childhood and subsequent development of temporal lobe epilepsy was established in a study of six families (Maher and McLachlan, 1995). The incidence of this problem is not known, but probably will be low. One should bear in mind that hippocampal sclerosis (HS) or MTS may be present in cases without seizures, and that MTS may be accompanied by other abnormalities, such as heterotopias and subtle migration defects. Pre-existing alteration of medial temporal lobe structures may contribute to febrile convulsions and subsequent hippocampal sclerosis (HS) in patients with temporal lobe epilepsy and antecedent FC. This is suggested by a family-study of FC with MRI investigations (Fernandez et al, 1998).

A follow-up MRI study of children with FC has provided evidence that prolonged FC can cause hippocampal sclerosis (VanLandingham et al, 1998).

The neuropathological results of studies of the human brain of patients who ever had generalized convulsive SE or died during or shortly after generalized convulsive SE confirm several results of animal experiments. Especially the predilection of neuronal damage to vulnerable regions such as hippocampus, cerebral cortex, thalamus and cerebellum is evident. A longer

duration of generalized convulsive SE, a younger age and the presence of medical complications appear to be related to the occurrence of neuronal damage (Scholz, 1951; Meyer et al, 1955; Small and Woolf, 1957; Peiffer, 1963; Norman, 1969; Rademecker et al, 1967; Rowan and Scott, 1970; Knopman et al, 1977; Veith, 1980; Corsellis and Bruton, 1983; Soffer et al, 1986; Leiffer et al, 1991; Mori et al, 1992; De Giorgo et al, 1992; Stafstrom et al, 1996; Fujikawa et al, 2000).

3.5 Status epilepticus in adult patients

3.5.1 Generalized Convulsive Status Epilepticus (GCSE)

The various studies about Generalized Convulsive Status Epilepticus (GCSE) are mostly retrospective, highly selective with patients from university hospitals or specialized neurological inpatient services, and with considerable differences in age groups (Rowan and Scott, 1970; Oxbury and Whitty, 1971; Heintel, 1972; Celesia et al, 1972; Aminoff and Simon, 1980; Celesia, 1983; Pilke et al, 1984; Goulon et al, 1985; Sung and Chu, 1989; Lowenstein and Alldredge, 1993). With respect to aetiology the distinction between cause and precipitating factor is not always clear; aetiology is often considered multi-factorial. Most studies do not make a distinction between causes in patients with previous epilepsy and those in which status is the first epileptic event; causes of status in pre-existing epileptic and previously non-epileptic cases are different (Shorvon, 1994). In the more recent studies, including the prospective series, other types of SE besides tonic-clonic are included (Goulon et al, 1985; Sung and Chu, 1989; DeLorenzo et al, 1996; Hesdorffer et al, 1998; Coeytaux et al, 2000; Knake et al, 2001). Finally, the duration of follow-up is highly variable (table 9). These limitations make it hard to compare the various studies with respect to outcome and cause of GCSE. From table 9 one may conclude that outcome in studies of SE with a high percentage of cases with previous epilepsy is better than in studies with high percentages of de novo SE. This is related to the underlying cause.
The most frequently occurring type of GCSE is TCSE. Other types of GCSE (tonic SE, clonic SE, myoclonic SE) have been described only occasionally because of their relatively rare occurrence (Gastaut, 1967; Roger et al, 1974; Celesia et al, 1988; Parisi and Shabrough, 1993; Shorvon, 1994; Othahara and Ohtsuka, 1997).

3.5.1.1 Tonic-Clonic Status Epilepticus (TCSE)

The most frequent type of GCSE is TCSE, which in most cases has a partial onset with secondary generalization. Some patients exhibit only partial or subtle signs of convulsive activity with a marked impairment of consciousness and bilateral ictal discharges on the EEG. These cases of subtle GCSE (Treiman, 1984) occur in patients with severe encephalopathies caused by underlying systemic illnesses, primary brain lesions such as massive cerebral infarctions or infections, or prolonged uncontrolled overt GCSE. The physiological changes in SE should be anticipated in order to prevent serious medical complications and consequently a worse prognosis (chapter 3.4).

TCSE can occur in patients with previous epilepsy (intercurrent SE), precipitated by systemic infections, non-compliance, sleep-deprivation and a miscellaneous group of more rare possibilities (Rowan and Scott, 1970; Heintel, 1972; Aminoff and Simon, 1980; Pilke et al, 1984; Janz, 1983; Goulon et al, 1985; DeLorenzo et al, 1992; Martin and Millac, 1994).

An acute symptomatic cause, such as a brain tumour or CVA, in a patient already known with epilepsy should be considered too (Aminoff and Simon, 1980; Goulon et al, 1985; Lowenstein and Alldredge, 1993). In a substantial number of cases the cause remains unknown. The most common mentioned precipitating factor in cases with previous epilepsy are non-compliance, alcohol and systemic infections (Janz, 1961; Rowan and Scott, 1970; Pilke et al, 1984; Aminoff and Simon, 1980; Leppik, 1990; Lowenstein and Alldredge, 1993; Martin and Millac, 1994; Coeytaux et al, 2000). Studies in both children and adults with SE have shown that low anti-epileptic-drug levels as a cause of SE may not be so frequent as presumed (Barry and Hauser, 1994; Maytal et al, 1996).

SE may also be the presenting sign of an acute symptomatic brain lesion (initial or isolated SE), especially in the older age group. Acute symptomatic causes are more prevalent in older age groups, with corresponding worse outcome (Celesia et al, 1972; Sung and Chu, 1989). The most often occurring causes are CVA, encephalitis, head trauma, brain tumour, metabolic disturbances and toxic causes, including alcohol (table 10). The reviews show no obvious differences with regard to the various possible causes, although the frequency of brain tumours as a cause of SE appears to decline. Lowenstein and Alldredge (1993) compared the causes during the

period 1980-1989 with the period 1970-1979, no apparent differences were mentioned. Recent population-based prospective studies have reported comparable causes of SE; these studies are difficult to compare because of differences in age distribution or exclusion of a certain cause. In all three studies no detailed distinction has been made with respect to cause between patients with or without previous epilepsy. (DeLorenzo et al, 1996; Coeytaux et al, 2000; Knake et al, 2001).

Table 9: Generalized Convulsive Status Epilepticus: characteristics from 14 studies

Author	Number	Age (yrs)	Previous Epilepsy (%)	Mortality (%)	Duration follow-up
Clark/Prout (1903/4)	42	10-60	100	14	Unknown
Oxbury/Whitty (1971)	86	11-80	71	8,1 14	End of status 6 months
Heintel (1972)	83	0-69	62	25	Discharge from hospital
Celesia (1972)	17	>40	35	35	3 months
Roger et al (1974)	100	20-60	44	37	End comatose phase
Aminoff/Simon (1980)	98	14-83	52	16	Unknown
Celesia (1983)	78	19-80	22	23	10 months
Pilke et al (1984)	71	16-80	83	2,4	Discharge from hospital
Goulon et al (1985)	282	>15	29	35	Unknown
Sung/Chu (1989)	102	>60	0	35	Unknown
Lowenstein/ Alldredge (1993)	154	17-98	56	14	Unknown
DeLorenzo et al (1996)	166	>30days 16-59 >60	42 54 30	22 14 38	30 days
Coeytaux et al (2000)	172	all	43	7,6	Discharge from hospital
Knake et al (2001)	150	>18	50	9,3	30 days

Outcome in TCSE

The early studies of SE reported the results from a period when treatment was rudimentary; they helped to define the natural history of TCSE in patients with previous epilepsy. Outcome in the early studies of SE was mentioned as mortality; morbidity was in most studies unrecorded. Mortality was especially high in institutionalised patients (35-50%). The seriousness of status was well recognized (Clark & Prout, 1903/4), but by no means universally fatal: in their study of 52 patients with 100 status periods, 14 died; a mortality rate of 14%. Despite improvements with regard to the care of patients with SE it is remarkable to note that recent studies of SE did not show a decline in mortality rate during the last 20-30 years (table 9). As has been discussed in the introduction of this chapter, several points must be stressed, however: most studies were retrospective, included different age groups and used different periods of follow-up. Furthermore it is important to mention that most figures have been derived from specialized hospital settings, where more severe cases have been treated, which may overestimate the risk of death (Hauser, 1990). This suggests that the published figures must be considered maximum estimates; this is also illustrated by the fact that especially in retrospective series cases with a short duration will have been missed and that therapy in early status will have been successful in most cases.

Table 10: Causes of initial and isolated TCSE (%)*

Author	Oxbury/ Whitty 1971	Roger 1974	Aminoff/ Simon 1980	Celesia 1983	Janz 1983	Pilke 1984	Goulon 1985	Sung/ Chu 1989	Lowenstein/ Alldredge 1993
Number of patients	24	56	48	43	93	14	201	102	67
CVA	16	12	23	16	15	43	20	35	6
Brain tumour	42	20	8	12	33	43	6	8	9
Head Trauma	4	39	4	18	17	14	3	21	9
Toxic	0	0	21	0	0	0	10	0	18
Metabolic	8	0	10	12	0	0	12	10	7,5
Encephalitis	21	0	8	2	13	0	10	2	15
Anoxia	0	0	0	5	0	0	18	0	9
Alcohol	0	0	8	12	0	0	0	0	21
Unknown	4	12	8	0	9	0	0	13	7,5
Other	4	17	0	23	13	0	20	11	0

* Cases of SE in patients with previous epilepsy are not mentioned.

The recent prospective studies did not entirely overcome the several problems present in the discussion about the risk of death in SE (DeLorenzo et al, 1996; Coeytaux et al, 2000; Knake et al, 2001). Mortality rates were reported irrespective type of status and the presence of previous epilepsy or not (table 9). The study in Virginia made a distinction with respect to outcome in age groups; the study in Switzerland gave an overall mortality percentage for all age groups, excluding cases with post-anoxic encephalopathy, which have a grave prognosis. Mortality in the Swiss group was 7,6%; the low rate was only partly explained by the exclusion of patients with post-anoxic encephalopathy, prompt and intensive therapeutic management in the pre-hospital setting was important too in reducing mortality (Coeytaux et al, 2000). The study in Germany reported a mortality rate of 9,3% in the adult patient, a percentage considerable lower than in Virginia. The lower mortality cannot be explained by differences in the populations that have been studied; the population in Virginia had a considerable non-white contribution, which was not the case in Germany. However, mortality in whites was higher (31%) than in non-whites (17%). Is also known that outcome in adult patients

from university hospitals is comparable to outcome in community based hospitals (DeLorenzo et al, 1992). A difference of importance with respect to outcome was the distribution of seizure types; in Virginia generalized (primary and secondary) SE was present in about 65% of the adult patients, in Germany in only 33,3% (table 5). A considerable percentage of patients in the German group were diagnosed as complex partial SE (43,3%), which has a better outcome than GCSE. Again this illustrates the importance of adequate differentiation of results with respect to outcome in the various groups of patients with different seizure types. An interesting study on long-term mortality showed that SE itself did not modify long-term mortality; mortality increased with duration and the presence of an acute symptomatic cause (Logroscino et al, 2002).

Another problem is how to calculate the relative contribution of the underlying cause and SE itself to outcome. In many cases this may be impossible to disentangle. Death attributed to SE itself has been reported by several authors, with percentages of only 1.3-2% (Oxbury and Whitty, 1971; Aminoff and Simon, 1980; Pilke et al, 1984; Lowenstein and Alldredge, 1993; Towne et al, 1994). It is not always clear why the cause of death has been attributed to SE itself; sometimes it is only mentioned that the patient died during or just after SE (Aminoff and Simon, 1980; Towne et al, 1994). In other reports specific medical complications have been mentioned, which occurred because of SE and caused death (Pilke et al, 1984; Lowenstein and Alldredge, 1993). Most reviews, however report only an overall mortality percentage with too little details for correct conclusions.

The same problems are present when discussing morbidity in TCSE. Ketz and Meier (1979) mentioned sequelae in 39% of 78 admissions, but only 9% appeared definitive. It was not mentioned, however, at what moment the sequelae had been considered definitive. In some reviews good outcome may also include minor neurological deficits (Lowenstein and Alldredge, 1993). Information from retrospective studies mentioned morbidity varying from 26% (Rowan and Scott, 1970) to 4.8% (Pilke et al, 1984). Rowan and Scott made no distinction between sequelae because of SE or underlying cause; they suggested that the longer the duration the higher the risk of morbidity. Oxbury and Whitty (1971) described 5 cases which undoubtly deteriorated after SE, two of them because of SE itself (one of them appeared

severely demented after SE). Aminoff and Simon (1980) described 12 cases with sequelae after SE, eight of them probably because of SE itself. Six of them showed intellectual impairment. Pilke et al (1984) mentioned one patient with ataxia, probably because of SE itself. A lower level of cognitive functioning after SE has been suggested by Dodrill (1986); a prospective study however, was less conclusive (Dodrill and Wilensky, 1990).

The development of epilepsy after an initial SE in children is usually associated with cerebral damage, often related to underlying pathology (Aicardi and Chevrie, 1970). The risk of epilepsy following SE in children is increased in acute and remote symptomatic cases, but not in idiopathic SE (Gross-Tsur and Shinnar, 1993). In adult patients less conclusive information is present about the risk of epilepsy following SE.

Controlling for age, sex and cause, acute symptomatic SE increased the risk for subsequent epilepsy 3,3-fold compared to brief acute symptomatic seizures (Hessdorffer et al, 1998). The risk of unprovoked seizures was related to the underlying cause: in anoxic encephalopathy the risk was 18,8-fold, in a structural lesion 7-fold and in metabolic causes 3-fold.

Recurrences of SE in adult patients occur in about 13% and in children in about 38%, especially when the patient is younger than 5 years, has neurological abnormalities and insufficient serum levels of anti-epileptic drugs (DeLorenzo et al, 1996). The recurrence rate in children is related to the cause of SE (Shinnar et al, 1992).

Prospective studies are needed which will be able to give more adequate information about morbidity because of SE itself. Recent prospective studies with MRI and neuron-specific enolase have provided interesting information about this subject.

Magnetic resonance imaging (MRI) studies of patients with SE have shown evidence of neuronal damage caused by SE itself. Both in children (Stafstrom et al, 1996; Tien and Felsberg, 1995; VanLandingham et al, 1998; Herrgard et al, 1999) and adults (Tien and Felsberg, 1995; Meierkord et al, 1997;Wieshman et al, 1997; Pohlmann-Eden et al, 2004) follow-up studies with neuro-imaging technics have shown that longstanding epileptic discharges can result in neuronal damage, especially in the hippocampus. Several types of SE have been mentioned: GCSE (Stafstrom et al, 1996), CPSE (Lansberg et al, 1999) and febrile SE (VanLandingham et al, 1998). The results of follow-up study with MRI were confirmed by the results of neuropathological examinations in a patient with refractory

GCSE (Stafstrom et al, 1996; Pohlmann-Eden et al, 2000; Pohlmann-Eden et al, 2004). MRI-volumetry in nine adult patients with SE did not show progressive volume reduction in the temporal lobe structures when treated promptly with a predetermined protocol (Salmenpera et al, 2000).

In the past less sophisticated means of neuro-imaging were available, such as pneumo-encephalography and CT-scan. Some studies suggested a relation between SE and neuronal damage (Aicardi, 1969; Gastaut, 1977; Aicardi and Chevrie, 1983).

Neuron-specific enolase (NSE) is a sensitive marker of brain damage (neuron damage, not glial cell damage) in stroke, global ischemia and coma. An increase of NSE in TCSE and CPSE has been established, but a firm relation between NSE and neuronal damage in SE in clinical studies has not been proven. The surprising finding of elevated NSE in absence SE (ASE) raises the question whether it can be a useful tool in the study of the relation between SE and neuronal damage (DeGiorgio et al, 1996; Correale et al, 1998; DeGiorgio et al, 1999).

Factors influencing outcome of TCSE

a. Aetiology

Outcome is especially determined by its cause (Whitty and Taylor, 1949; Rowan and Scott, 1949; Oxbury and Whitty, 1971; Heintel, 1972; Celesia, 1983; Goulon et al, 1985; Delanty et al, 2001; Claassen et al, 2002). Outcome in cases with previous epilepsy is much better (Shinnar, 1993; Lowenstein and Alldredge, 1993; Barry and Hauser, 1993). Mortality in patients with previous epilepsy was 16%, in patients without previous epilepsy, with a high percentage of acute symptomatic causes; mortality was 61% (Barry and Hauser, 1993). Some causes, such as anoxia and hypoxia, have a worse outcome in comparison to other causes (Treiman, 1993; Towne et al, 1994). A retrospective study showed that anoxia had the worst prognosis with a mortality rate of 80%; other causes with a bad prognosis were stroke and metabolic abnormalities (mortality of 70%). Causes with a relatively good outcome were trauma, anticonvulsant withdrawal and alcohol abuse (Shinnar, 1993; Lowenstein and Alldredge, 1993; Towne et al, 1994). Comparable results were found during a prospective study of SE (DeLorenzo et al, 1995). In cases (alcohol abuse; low anti-epileptic drugs; no apparent cause) without clear risk factors for persistent organ vulnerability that

might lead to death, it is reasonable to presume that death may be related to the seizure activity of SE.

A prospective study showed that the presence of certain co-morbidities in adults was related to higher mortality (anoxia 68%, sepsis 55%, tumour 54%). Mortality increased as the number of co-morbidities increased, especially in adults (Towne et al, 1999). The presence of cardiovascular disease increased mortality, especially in children (Garnett et al, 2000).

Outcome is especially determined by the underlying cause, but SE may also worsen the prognosis of the underlying condition. In their study of patients with SE admitted to the intensive care unit, Goulon and colleagues (1985) mentioned a mortality rate of 33% in cases with bacterial meningitis without and of 82% in cases with SE. A comparable result was noted in cases of SE caused by CVA; morbidity in cases with CVA and SE increased three times in comparison to cases with only a CVA and eight times to cases with only SE and no CVA (Waterhouse et al, 1998). It is difficult however, to ascertain to what extent excess mortality was due to SE or whether SE simply reflected a greater severity of the underlying condition.

b. Duration of TCSE

In experiments using rats duration of 30 minutes appeared to be a limit beyond which pathophysiologic changes occurred (Nevander et al, 1984; Nevander et al, 1985). In humans it is difficult to differentiate the independent effects on outcome of underlying cause and duration of SE. Some clinical studies have provided evidence of a relation between duration of SE and outcome (Rowan and Scott, 1970; Heintel, 1972; Ketz and Meier, 1979; Aminoff and Simon, 1980; Barois et al, 1985; Towne et al, 1994; DeLorenzo et al, 1999).

Neither Rowan and Scott (1970) nor Aminoff and Simon (1980) did find complications in patients with duration as long as 90 or 120 minutes. There was an important increase in morbidity if cases lasted 10 hrs or more, and of mortality in cases lasting 13 hrs or more (Rowan and Scott, 1970). A poor outcome was more likely as duration of SE increased; insufficient data were, however, available to permit firm conclusions about the relationship between duration and outcome (Aminoff and Simon, 1980).

The retrospective study by Heintel (1972) reported a significant increase of mortality when duration of SE exceeded 6 hours. Ketz and Meier (1979)

indicate that 6 hours is a critical period after which permanent neurological morbidity was apt to occur.

Mortality was 4% in 51 cases with duration of 30 minutes-24 hours; morbidity and mortality was however, 24% each in 29 cases with duration of more than 24 hours (Barois et al, 1985). Mortality in adult patients was only 2,7% in cases with a duration of 1 hour or less, whereas mortality was 32% in cases lasting over one hour (Towne et al, 1994).

Outcome in patients with prolonged seizures (10-29 minutes) was compared to outcome in patients with SE (DeLorenzo et al, 1999). Mortality in patients with prolonged seizures was significantly lower than in SE. Adult patients and elderly, children however not, may die having prolonged seizures; mortality increases significantly with duration, especially in the elderly. In the elderly aetiology was not different in both groups, duration was therefore important with regard to outcome.

Long-term risk for mortality was increased in cases with duration of 24 hours or more in comparison to cases with duration of less than 2 hours (Logroscino et al, 2002)

The relation between outcome and duration should be discussed separately for cases where outcome is determined by the underlying cause and cases where SE itself has been the main determinant. When outcome is especially determined by the underlying cause, damage is present from the start of SE and the contribution of continuous seizures will be hard to establish. Although several authors have established a relation between duration and outcome, only one paper used the distinction between underlying cause and SE itself in reporting the relation between outcome and duration of GCSE (Aminoff and Simon, 1980).

c. Therapy

First line drugs, such as benzodiazepines and phenytoin, are successful in 80% of the cases of SE when therapy is started within 30 minutes after the start of the seizures; when therapy is started after 2 or more hours, first line therapy fails in 60% of the cases (Walton and Treiman, 1988; Lowenstein and Alldredge, 1993). Therapy delay contributes to a longer duration of SE (Whitty and Taylor, 1949; Rowan and Scott, 1970; Treiman et al, 1983; Lowenstein et al, 1988). This is also the case for inadequate therapy (Delgado-Escueta and Enrile-Bascal, 1983; Celesia, 1983). The significance

of early treatment with respect to duration of SE has also been illustrated by a retrospective evaluation of pre-hospital treatment in children with TCSE; a significant decrease of duration of SE, of the recurrence rate and of duration of hospital stay was established (Alldredge et al, 1995). Improved outcome because of pre-hospital treatment were suggested in the prospective Swiss study (Coeytaux et al, 2000).

These results suggest an indirect relation between therapy and outcome; therapy delay and quality of therapy are related to duration of SE and because of this relation indirectly to outcome.

The effects of delayed treatment and time to respond to therapy on mortality were studied using multi-regression logistic analysis in 242 adult patients with GCSE. Both the response to initial therapy and the time to initial therapy were important factors in predicting mortality (DeLorenzo et al, 1998).

d. Age

Mortality increases with age (Celesia, 1972; Sung and Chu, 1989; Barry and Hauser, 1993; Towne et al, 1994; Delorenzo et al, 1996; Claassen et al, 2002). Highest mortality rates are present in the elderly with corresponding high percentages of acute symptomatic causes. Prognosis of SE in the neonate is also especially determined by cause, mortality rates are also very high. Mortality in children is 2,5%, in children less than 1 year mortality is considerable higher, 13,2% (DeLorenzo et al, 1996; Morton et al, 1998). Aicardi and Chevrie (1970; 1983) found that death and sequelae of SE were more common in younger infants; the incidence of death and sequelae declined from 77% in children of less than 6 months to 46% of older than 3 years. This was not entirely related to the more frequent occurrence of symptomatic status in younger patients: sequelae after cryptogenic SE occurred in 35% in children less than 3 years, and in 9% in children older than 3 years.

Although a relation between age and incidence of sequelae was noted, it appeared a reflection of the fact that acute symptomatic SE was far more common in the younger age group (Maytal et al, 1989). A stepwise regression procedure was used to study the influence on outcome of factors independently; age was not significantly related to outcome in children (Dunn, 1988; Maytal et al, 1989). It seems more likely that the range of causes in children and adults and not age influences outcome.

e. Miscellaneous

Outcome was prospectively investigated in 212 children and 433 adults in relation to type of SE: continuous versus intermittent. In adults the continuous type was negatively correlated to mortality; in children this was not the case. The difference in mortality in the continuous versus the intermittent type was not determined by cause, age, seizure type or duration (Waterhouse et al, 1998).

Outcome in adult patients appeared worse in cases with high serum levels of cortisol (Calabrese, 1993) or high levels of CSF lactate (Calabrese, 1992).

A genetic factor with respect to outcome may be suspected. A genetic predisposition to SE has been suggested by twin studies (Corey et al, 1998; Corey et al, 2004) and by the higher incidence in non-whites versus whites (DeLorenzo et al, 1996). Mortality in whites, on the other hand, appeared higher (31%) than in non-whites (17%). Another suggestion to a genetic factor in relation to outcome is the genetically determined GABA-A receptor subunits combination, which shows a rapid modification of its functional properties during status, resulting in a rapid loss of efficacy of benzodiazepines. A genetic factor may explain some of the puzzling questions with respect to the relation between outcome and SE. Until now no information is present to allow more than a suggestion in this respect.

Prognosis in GCSE is particularly determined by the underlying cause; other important factors are duration of SE of more than 1 hr and a continuous type of status. Less conclusive, but at least contributing to poor outcome, are therapy delay, inadequate therapy and the presence of medical complications and/or co-morbidity.

Electroencephalographic recording in TCSE

In the literature little information is present about electroencephalographic findings in TCSE (Roger, 1974; Stefan, 1990). The EEG in TCSE in the early stages shows the classic pattern of isolated tonic-clonic seizures with onset of discharges on one side of the scalp in 57% of the cases, whereas in 43% of the cases the onset is bilaterally synchronous and symmetrical (Roger et al, 1974). The post-ictal depression that commonly follows an isolated generalized tonic clonic seizure was seen in only 46% of the cases.

A distinctive five-phase temporal evolution in EEG patterns during SE has been suggested (Treiman et al, 1990; Handforth et al, 1992; Lothman and Bertram, 1993). The following phases are distinguished:

1. Discrete seizures with inter-ictal slowing (clinically tonic-clonic seizures).
2. Merging seizures with waxing and waning of amplitude and frequency of EEG rhythms (clinically most often focal intermittent tonic and/or clonic convulsive activity).
3. Continuous ictal discharges (clinically continuous generalized clonic jerks or subtle clonic movements).
4. Continuous ictal discharges with flat periods (clinically overt or subtle focal clonic movements or no motor symptoms).
5. Periodic epileptiform discharges (PED) on a flat background.

Retrospective studies could not confirm this typical temporal evolution (Lowenstein and Aminoff, 1992; Nei et al, 1999). Some patients remained in pattern I of Treiman, no matter the duration of SE. A prospective study with serial EEG reported increased mortality in cases with PED's, although cases of SE with PED's caused by non-compliance or metabolic disturbances had good outcome (Garzon et al, 2001). A predictable sequence of EEG patterns was not found. In one third the same pattern persisted until resolution of status, and in another one third the SE had already resolved at the second EEG. The remainder showed a variable EEG pattern without a stereotyped sequence. PED was the initial pattern in 14 of 62 SE episodes, a relation between duration of status and the incidence of PED' was not present. PED appeared an ictal pattern, which disappeared after treatment, with clinical improvement. Other initial EEG patterns were intermittent EEG seizures or discrete seizures (44%), merging seizures (18%), and continuous ictal discharges (16%).

In patients with altered consciousness it may be difficult to determine whether the underlying cause or SE is the cause of the altered consciousness (Privitera et al, 1994). In 74 patients with altered consciousness the EEG confirmed the diagnosis of SE: in 42 patients complex partial SE, in 3 myoclonic SE and in 29 subtle GCSE. Most cases with subtle GCSE concerned a diffuse brain injury rather than evolving from convulsive SE. No significant relationship could be determined between the EEG pattern (intermittent or continuous EEG spiking) and duration of subtle GCSE (Privitera et al, 1994).

A retrospective study reported the results of emergent EEG in a hospital over a period of 52 months (Varelas et al, 2003). The most common reason to order the EEG was a change in mental status or coma, especially to rule out SE. In 10,7% of these cases SE was present. A history of cardiac or respiratory arrest was the only independent risk factor for SE.

EEG monitoring in SE is important too with regard to the evaluation of therapy, especially when the patient is artificially paralysed and mechanically ventilated. Persistence of electroencephalographic SE after disappearance of overt clinical signs should also be anticipated. The EEG is probably under-utilized among patients with SE. It was calculated that during the period 1988-1995 only 11% of the patients with SE had an EEG during hospitalisation (Trevathan and Rurangirwa, 1999).

A prospective study of EEG monitoring after SE revealed various patterns. Good outcome was present in cases with a normal EEG, whereas poor outcome was found in cases with burst suppression, after-status-ictal-discharge (ASIDS) and to a lesser extent with PED's, also after correction for aetiology. This study showed persistent ictal activity despite control of clinical seizure activity and stresses the importance of EEG monitoring to determine treatment effects (Jaitly et al, 1997). A prospective EEG study in 164 patients, older than 16 years, showed despite disappearance of overt clinical signs of GCSE in 14% persistent intermittend or continuous non-convulsive SE (NCSE). Mortality in this group (51%) was significantly higher than in cases without NCSE (13%), corrected for age and aetiology. Therapy was not evaluated, aggressive treatment of NCSE was suggested to improve outcome (DeLorenzo et al, 1998).

In patients with GCSE a burst suppression pattern on the EEG has been used as a target for the titration of barbiturate or anaesthetic therapy. It is not clear from what source this strategy arises; no studies are available which show a

relation between achieving or maintaining burst suppression and outcome. One study suggested better results of attaining a flat record in comparison to burst-suppression in patients with SE treated with barbiturate anaesthesia (Krishnamurthy and Drislane, 1999). A literature study suggested better results of background suppression (burst suppression or flat records) with pentobarbital in comparison to suppression of seizures with midazolam or propofol (Claassen et al, 2002)

Burst suppression (BS) is a periodic EEG pattern characterized by bursts of spikes, sharp and slow wave activity during 1-5 sec. followed by periods of 2-9 sec. of electrical silence, without variations during either waking-sleeping status or sensory stimulation. In the pre-term neonate (24-36 w) BS may be a normal physiological pattern, but in the a-term neonate (and later) BS is always an abnormal pattern expressing an anatomical or functional (barbiturate anaesthesia) disconnection between cerebral cortex and deeper structures. One should consider two points when one takes BS as guideline for barbiturate anaesthesia. First there is a potential of severe hypotension with a risk of increased morbidity and mortality (Yaffe and Lowenstein, 1993). Second epileptic discharges can sometimes remain present despite BS. One wonders whether a lower dose would be sufficient too, especially when one considers the fact that seizure related neuronal injury is related to high-frequency repetitive discharges and not to isolated spike activity (Lowenstein et al, 1990). Prospective investigations are necessary to find out whether a BS pattern is a necessary requirement for sufficient barbiturate anaesthesia.

For a particular individual it is not possible to reliably predict the EEG characteristics during status, because of differences in underlying cause, systemic physiologic changes and drug treatment, which will all influence the EEG. The suggested temporal evolution in EEG patterns during status has not been acknowledged by other studies; a considerable portion of the patients remain in a fixed pattern. Some EEG patterns suggest a poor outcome, such as PED or burst-suppression.

3.5.2 Nonconvulsive Status Epilepticus in adult patients

3.5.2.1 Introduction

Prolonged epileptic states without convulsions have been described before the EEG era (Clark and Prout, 1903/4). It was not until the introduction of the EEG that further progress in understanding these conditions was possible. Non-convulsive Status Epilepticus (NCSE) is characterized by a clouding of consciousness, confusion, automatisms and amnesia, with in accordance to the type of NCSE, specific EEG abnormalities. In most cases there is a clinical evident alteration from baseline in mental status or behaviour, together with seizure activity on the EEG. The diagnosis NCSE is not always apparent; the clinical presentation may be mistaken for a psychiatric disorder (hallucinations- laughing-crying-confusion), a metabolic encephalopathy (confusion), post-ictal (lethargy), intoxication, or attributed to an infection, a stroke or a brain tumour (Kaplan, 1996; Drislane, 1999). This may lead to significant delay in the correct diagnosis or the diagnosis may even be omitted entirely, when EEG investigation is not considered (Kaplan, 1996; Jordan, 1999; Towne et al, 2000). This is especially the case in certain patient groups, who show changes in the level of consciousness without overt clinical seizure activity, of unknown cause. Examples of these patients are patients with mental retardation (Shorvon, 1994), patients admitted to the Intensive Care Unit (Young et al, 1996; Litt et al, 1998) and patients without manifest clinical signs after generalised convulsive SE (Fagan and Lee, 1990; DeLorenzo et al, 1998). In patients with changes in consciousness, with or without subtle motor activity, EEG investigation should be considered, despite the presence of an acute brain injury (Privitera et al, 1994; Jordan, 1999). Prolonged EEG recording was 5 times more likely to identify NCSE than routine EEG (Varelas et al, 2003). The EEG is in most cases conclusive, but sometimes difficult to interpret (Kaplan, 1999) or the scalp EEG may show only minor changes, whereas depth EEG recording may show CPSE (Williamson et al, 1985). In summary, one should consider NCSE in the following clinical conditions:

- Apparent prolonged postictal state.
- Prolonged reduction of alertness from an operative procedure or neurological insult.

- Impaired mentation or consciousness with myoclonus of facial muscles or nystagmoid eye movements.
- Acute onset of impaired consciousness or fluctuating picture with episodes of normal mentation.
- Episodic blank staring, aphasia, automatisms, perseverative activity.
- Aphasia without any structural lesion.
- Other acutely altered behavior without other obvious etiology.

A suspicion of NCSE is the most important clinical indication for performing an EEG. When EEG monitoring is not possible, some features are highly suggestive for NCSE, such as remote risk factors for seizures, impaired mental status and ocular movement abnormalities (Husain et al, 2003).

In adult patients NCSE is divided in two main groups, Generalized Non-Convulsive Status Epilepticus (GNCSE) and Complex Partial SE (CPSE), which because of their clinical similarities have been discussed together by most authors. GNCSE includes Absence SE (ASE) and atypical ASE; the latter occurs especially in patients with symptomatic generalized epilepsy and mental retardation.

3.5.2.2 Absence Status Epilepticus (ASE)

ASE confirmed by EEG was described first by Lennox in 1945, since then several reports have appeared which describe ASE under a variety of names: Absence SE, petit mal SE, epilepsia minor continua, spike-wave stupor and prolonged petit mal automatisms (Shorvon, 1994). At the moment absence status epilepticus (ASE) is the most frequent used term to describe a prolonged confusional state of varying severity, with a fluctuating level of consciousness together with generalized paroxysmal spike-wave activity on the EEG (Lob et al, 1967; Andermann and Robb, 1972; Karbowski, 1976; Porter and Penry, 1983; Guberman et al, 1986; Dunne et al, 1987). Clinically and electroencephalographically a continuous and a discontinuous type may be distinguished. Duration of ASE varies from 30 min. to 1 or 2 days (Lob et al, 1967; Bauer, 1975; Rohr-Le Floch et al, 1988). Most cases have duration of less than 12 hrs (Lob et al, 1967; Guberman et al, 1986; Tomson et al, 1986; Tomson et al, 1992). The EEG in typical ASE shows generalized continuous paroxysmal activity without focal features. Although the 3 Hz spike-wave discharges are the best-known EEG abnormalities, other frequencies are

possible too, varying from 0.5 - 6 Hz, regular or irregular (Porter and Perry, 1983).

ASE in patients with *previous epilepsy* may be precipitated by tonic-clonic seizures, anti-epileptic drug withdrawal, systemic infection, fatigue and stress, or may be related to the menstrual or sleep-waking cycle (Andermann and Robb, 1972; table 11).

Typical ASE in syndromes of idiopathic generalized epilepsy (IGE) in 21 adult patients showed a mean age of onset of ASE of 29,2 years, range 9-56 years (Agathonikou et al, 1998). The mean number of episodes was 10,9 (1-40). The mean minimal duration was 3,7hrs (30min-24hrs), the mean maximal duration 26,5hrs (30min-10days).

The most important clinical symptom was slight-moderate lowered consciousness, with withdrawal, slow ideation, confusion, slowness of responses and sometimes experiential phenomena. A fluctuating level of consciousness was in only 5 cases present. Myoclonic jerks were found in 9 patients (peri-oral or eyelid, limbs). Amnesia was variable, complete in only 1 patient. In 8 patients ASE preceded GTCS; in 7 patients ASE was the first sign of epilepsy. An important finding was the fact that ASE was recognized as such in only 4 cases. In 10 patients ASE was ignored. In 3 patients ASE was misdiagnosed as depression, in 2 as CPSE and in 2 as post-ictal confusion. During follow-up study of 3-7 years all but three were free of further episodes of ASE for more than 2 years. The majority were taking valproate.

In cases *without previous epilepsy* ASE may be the only or initial presentation of idiopathic generalized epilepsy, or occur de novo in elderly patients (Amand, 1971; Schwartz and Scott, 1971;Wells, 1975; Ellis and Lee, 1978; Bateman et al, 1983; Aguglia et al, 1983; Bourrat et al, 1986; Terzano et al, 1986; Thomas et al, 1992). A second group consists of ASE as a situation related generalized NCSE, caused by e.g. drug withdrawal or by toxic drugs (Pritchard and O'Neal, 1984; Elian and Fenwick, 1985; Vollmer et al, 1985; Emre and Baumgartner, 1985; Ahmed et al, 1988; Obeid et al, 1988; Sweden and Mellerio, 1988). An example of situation related generalized NCSE is ASE caused by metrizamide (Pritchard and O'Neal, 1984; Obeid et al, 1988). Other toxic causes included tricyclic antidepressants, aliphatic neuroleptics or combinations of both (Sweden and Mellerio, 1988). Examples of drug withdrawal concerned especially abrupt withdrawal of benzodiazepines

(Emre and Baumgartner, 1985; Sweden and Mellerio, 1988). De novo ASE in the middle-aged and the elderly (table 12) occurs mostly in females, without a history of previous epilepsy (Amand, 1971; Thomas et al, 1992). Some are known with previous IGE and develop ASE after a seizure free interval of many years. Those without previous epilepsy have in most cases an age of more than 60 years (Richard and Brenner, 1980; Sundaram and Lowry, 1985). Although in some cases a frontal origin is suggested by the electroencephalographic findings (Ellis and Lee, 1978; Aguglia et al, 1983; Bourrat et al, 1986), a structural damage has not been found. The clinical presentation may be highly suggestive of a psychiatric diagnosis; in many patients a prolonged confusion was accompanied by paranoia and hallucinations (Wells, 1975; Ellis and Lee, 1978; Bateman et al, 1983; Bourrat et al, 1986). Precipitating factors are mentioned in table 12.

Incidence of ASE

The incidence of ASE is hard to estimate; not all cases are recognized and not all cases will be admitted. A history of ASE in patients with generalized absence seizures is said to occur in 5-10% of the cases with absence epilepsy (Shorvon, 1994). An annual incidence of ASE was calculated at 1 per million of the general population. Recent prospective studies found higher incidence rates, varying from 4-10 per million (DeLorenzo et al, 1996; Coeytaux et al, 2000; Knake et al, 2001); the highest incidence rate was in a study restricted to only adult patients (Knake et al, 2001).

Males and females seem equally affected; the condition tends to develop in the young: most cases are younger than 20 years.

The occurrence of 21 cases of typical ASE in syndromes of idiopathic generalized epilepsy (IGE) in 136 adult patients in 5 years suggested a prevalence of ASE in IGE of 15,4% (Agathonikou et al, 1998). ASE occurred in 24,4% of cases with typical absences alone or in combination with other seizure types. The prevalence of typical ASE appeared to be syndrome related.

Therapy of ASE

Therapy of ASE, including situation related generalized NSE and ASE de novo in the elderly, but with the exception of atypical ASE, is prompt and successful in most cases. The drugs that are used most are benzodiazepines, such as diazepam (Bauer et al, 1982; Guberman et al, 1986; Dunne et al, 1987), clonazepam (Kiefer et al, 1982; Dunne et al, 1987) and clobazam (Tinuper et al, 1986). Only one study compared two drugs in ASE, clonazepam and diazepam (Bülau et al, 1986). The results of both drugs were comparable, but less adverse events were mentioned after clonazepam use, in comparison to diazepam. Anti-epileptic maintenance therapy is hardly necessary in the other elderly patients with ASE de novo (Bourrat et al, 1986, Thomas et al, 1992).

Episodes of ASE or GCSE in patients with IGE treated with carbamazepine and/or phenytoine at therapeutic concentrations were more frequent and proved intractable to treatment with valproate or benzodiazepines compared to cases treated otherwise (Osorio et al, 2000).

3.5.2.3 Complex partial Status Epilepticus (CPSE)

The first description of CPSE authenticated by EEG was in 1956 by Gastaut (Gastaut et al, 1956). The clinical presentation has been described extensively (Treiman and Delgado-Escueta, 1983; Wieser et al, 1985; Tomson et al, 1986; Dunne et al, 1987; Rohr-Le Floch et al, 1988; Tomson et al, 1992). CPSE is a prolonged epileptic episode in which fluctuating or frequently recurring focal electrographic epileptic discharges, arising in temporal or extra temporal regions, result in a confusional state with variable clinical symptoms (Shorvon, 1994). Important is the distinction between a continuous type, characterized by long-lasting confusion with or without psychotic behaviour or automatisms and continuous focal discharges and a discontinuous type with recurrent complex partial seizures with circumscribed discharges as seen in single complex partial seizures, however without recovering of consciousness between the seizures (cycling type). Most cases with CPSE (75%) occur in patients with previous epilepsy. A greater part (about 80%) of the patients shows automatisms, whereas convulsive signs are present in only 35%. A discontinuous type occurs more often (60%) than the continuous type. A male or female preference has not been noted. In cases with previous epilepsy most patients are between 20 and 50 years of age,

in cases without a previous history of epilepsy a preference is present for patients older than 50 years.

Prolonged confusion and/or psychosis may be the main manifestation of CPSE of extra-temporal (e.g. frontal lobe) origin or may occur at the end of the cycling type. The cycling type may originate from the temporal lobe with primary or secondary involvement of the amygdalo-hippocampal region, but an extra temporal origin is also possible (Delgado-Escueta and Treiman, 1987). A clinical distinction between CPSE of frontal or temporal lobe origin was suggested by Rohr-Le Floch (Rohr-Le Floch et al, 1988). CPSE of frontal lobe origin was characterized by confusion and behaviour disturbances, whereas CPSE of temporal lobe origin showed confusion and emotional disturbances. A recent prospective study described NCSE of frontal origin in 10 patients in 5 years from a total of 44 cases with NCSE (Thomas et al, 1999). The delay in diagnosis was 48 hours (3-96hrs). Three were referred to the psychiatric ward (hypomanic state, hysteria), one was diagnosed as transient global amnesia, one as alcohol-related. Two groups were described: the first group consisted of 7 patients with mood disturbances in combination with affective disinhibition or affective indifference and subtle impairment of cognitive function without overt confusion. The EEG showed unilateral frontal ictal pattern and a normal background. The second group included 3 cases with impaired consciousness, associated with bilateral frontal EEG discharges and abnormal background.

Duration of CPSE varies from 30 min. to 2 weeks; about 40% has a duration of less than 24 hrs, another 40% 1 to 10 days. A case of exceptional long duration, 7½ months, has been described (Roberts and Humphrey, 1988).

The clinical diagnosis of CPSE may be difficult; EEG investigation is essential in order to differentiate from e.g. ASE. EEG investigation in CPSE, however, is not always conclusive; depth-recording may reveal CPSE, whereas scalp recording did not show specific EEG abnormalities (Wieser, 1980; Wieser et al, 1985; Williamson et al, 1985). In most cases however, surface recording shows specific epileptic activity, such as continuous temporal spikes or spike-wave activity, or there are recurrent seizures with or without secondary generalisation.

The various causes and precipitating factors of CPSE are mentioned in table 11 and 12.

Incidence of CPSE

Little is known about the incidence of CPSE. A study in Sweden found an incidence of NCSE in adult patients of 1.5 per 100,000 inhabitants; one can calculate an incidence of CPSE of 0.67 (Tomson et al, 1992). At least 15% of patients with active complex partial epilepsy have a history of non-convulsive episodes (Shorvon, 1994). An annual incidence of CPSE was calculated to be 3.5 per 100,000. The prospective study in Virginia found an incidence of 1.2 per 100,000; significant case under ascertainment was however present (DeLorenzo et al, 1996). In a recent prospective study (all age groups), including EEG investigation, an incidence of 4.4 per 100,000 was suggested; this number dropped to 2.8 when areas were included with less perfect case-ascertainment (Coeytaux et al, 2000). From a prospective study in adults an incidence of 6.9 per 100,000 could be calculated (Knake et al, 2001). Extrapolating the number from Switzerland to the Netherlands one may expect at least 700 cases of CPSE every year.

Treatment of CPSE

Treatment consists in most cases of phenytoin and/or benzodiazepines. Other drugs consisted of phenobarbital, carbamazepine, thiopental, chlormethiazole or no therapy at all.

Table 11: Precipitating factors and causes of CPSE and ASE in patients with previous epilepsy, as mentioned in the literature*

Previous Epilepsy	CPSE (83 cases)	ASE (97 cases)
Following tonic-clonic seizure	9	29
AED withdrawal and non-compliance	6	16
AED withdrawal (presurgical evaluation)	14	--
Systemic infection	1	5
Systemic surgery	2	0
Menstrual cycle, pregnancy	4	7
Sleep-deprivation, fatigue, minor trauma, hyperventilation	0	8
Alcohol	1	5
Intoxication	1	1
CVA	0	1
Trauma	1	0
Brain tumour	1	0
Unknown	43	25

* Absolute numbers

Table 12: Causes and precipitating factors of CPSE and ASE in patients without previous epilepsy as mentioned in the literature*

No previous epilepsy	CPSE (61 cases)	ASE (44 cases)	ASE de novo in the elderly (55 cases)
Intoxication	0	18	13
Crack-cocaine	2	0	0
Drug withdrawal (no AED)	2	16	11
Thyroxine	0	2	0
Electroshock therapy	0	1	0
Fatigue	0	1	0
Metabolic disturbance	0	0	6
Heart failure	0	0	1
Lymphoma	0	0	1
Systemic surgery	0	0	1
CVA	24	0	0
Brain surgery	3	0	0
Alcohol	2	0	1
Brain tumour	6	0	0
Encephalitis	4	0	0
Leptomeningeal carcinomatosis	1	0	0
Following tonic clonic seizure	2	0	0
Pregnancy	1	0	0
Unknown	14	6	21

* Absolute numbers

3.5.2.4 Special clinical conditions and NCSE

NCSE may be present in patients with coma without overt clinical seizure signs. A prospective study in 236 patients reported 19 cases (8%) with NCSE; no difference was present in outcome or causes between cases with or without NCSE (Towne et al, 2000).

The relation between outcome and presence of NCSE in elderly patients admitted to the ICU with unexplained impairment of consciousness remained unclear (Litt et al, 1998). Treatment of NCSE with benzodiazepines was even negatively correlated with outcome; this was also true for the presence of generalized epileptic discharges.

Apart from coma, other clinical features in acute brain injury may be caused by NCSE: aphasia, mental dullness, limb posturing, abnormal eye movements, automatisms and cortical blindness (Jordan, 1999). The diagnosis is often unsuspected; the most common presentation is non-localising coma.

When adequate recovery after an acute brain lesion such as stroke or after seizures does not occur one should consider NCSE, also in cases without obvious clinical seizure activity; improvement may be expected after therapy with AED (Hilkens and de Weerd, 1995; Drislane, 1999; Claassen et al, 2004). Especially in comatose patients prolonged EEG recording (>48 hours) may be necessary to detect seizure activity (Claassen et al, 2004).

Patients with unexplained or protracted impairment of consciousness or altered behaviour after a recognized seizure or GCSE, without overt clinical seizure signs may have NCSE (Fagan and Lee, 1990;Young et al, 1996; Delorenzo et al, 1998; Claassen et al, 2004). Mortality in cases with NCSE was significantly higher than in cases without NCSE (Young et al, 1996; Delorenzo et al, 1998). Aggressive treatment of NCSE in these cases was suggested (Delorenzo et al, 1998).

3.5.2.5 Outcome in NCSE

ASE may show a high incidence of recurrence (Agathonikou, 1998; Guberman, 1986).

Outcome is good in all cases; there is no evidence for morbidity or mortality in ASE.

Valproic acid prevented recurrence of ASE in a high percentage of patients (Berkovic et al, 1989; Agathonikou et al, 1998).

Mortality in NCSE (various types) appeared to be determined by acute symptomatic causes, the development of acute complications and severe mental status impairment, but not by the type of EEG discharges (Shneker and Fountain, 2003).

Most cases with CPSE and morbidity concern patients with acute brain injuries; neurological morbidity in cases with previous epilepsy is mostly mild and usually improves. Outcome is worse in cases with severe neurological damage, whereas in ambulatory cases outcome is in most cases good (Kaplan, 1996; Cockerell et al, 1994). One should also consider the risk of recurrence (Cockerell et al, 1994). The risk for new-onset ASE and

CPSE resulting in chronic epilepsy has not been looked at systematically. Neuropathological studies of the effect of SE in humans are scarse; most fatal cases are often caused by acute brain injuries. This is especially the case in CPSE, because most cases are not fatal, unless associated with acute brain injuries. Experimental results in animals have shown that CPSE may cause selective neuronal damage, especially in the CA1 and hilar region of the hippocampus and in the thalamus (Lothman, 1990; Meldrum, 1993; Ben-Ari, 1997). The fact that only few reports exists with morbidity in humans is in contrast with the data in animal experiments.

Outcome of NCSE in patients with coma without clear or very mild clinical seizure findings is especially determined by the underlying cause; the presence of NCSE in these patients appears to have little influence on outcome (Lowenstein and Aminoff, 1992; Litt et al, 1998; Towne et al, 2000). In this borderland group the epileptic EEG changes merely reflect damage from severe brain injuries. This is not the case in patients with NCSE after disappearance of overt clinical signs of GCSE (DeLorenzo et al, 1998). Outcome in these patients is worse than in those without NCSE. Aggressive treatment has been advised, but results are not present.

In GCSE the prognosis of the underlying condition may worsen because of the presence of SE (Goulon et al, 1985; Waterhouse et al, 1998). Whether such an effect is present between NCSE and acute brain injury with respect to morbidity and mortality has not been proven. On the other hand acutely injured neurons are more likely than intact neurons to suffer irreversible injury or death when exposed to comparable levels of ischaemic, metabolic or hypoxic insults (Miller and Becker, 1982). It is obvious that guidelines are necessary for the intensity and duration of anticonvulsant therapy in these cases.

What is the evidence for morbidity in CPSE because of the epileptic discharges themselves in humans?

a. Clinical case reports

Some case-reports mentioned prolonged memory deficits after CPSE, although it was not proven that this deficit was permanent (Engel et al, 1978; Kitagawa et al, 1979; Guerreiro et al, 2001). One patient was left with delusions, requiring psychiatric care after CPSE (Rossum et al, 1985). Duration of follow-up was not mentioned. A prospective study with complete

neuropsychologic testing before and after SE demonstrated worsening in 4 cases with GCSE and 5 with CPSE. The differences were, however, not significant (Dodrill and Wilensky, 1990). Serious morbidity and mortality has been reported in 10 cases with CPSE (Krumholz et al, 1995). Three patients died (2 of unknown cause, 1 CVA), 4 cases showed morbidity because of the underlying cause. Following CPSE three patients with previous epilepsy developed memory deficits and in two cases also cognitive loss. The authors considered morbidity caused by status itself and was permanent in one patient, and persisted for more than 2 years respectively 6 months in the other two cases.

Apart from the duration of CPSE, which in most cases of sequelae presumed to be caused by CPSE itself was more than 24 hrs, therapy delay or inadequate therapy may have been important too; e.g. a patient with delusions after CPSE with a duration of 3 days had not been treated (Rossum et al, 1985); another patient with CPSE of more than 20 hrs who showed a memory deficit and hallucinations after recovery from CPSE had been treated after a considerable delay (Kitagawa et al, 1979).

b. Neuron-specific enolase (NSE)

NSE is a sensitive marker of brain damage in stroke, global ischaemia and coma. Several studies have reported increased levels of NSE in CPSE and ASE, the relation between morbidity and SNE levels, however, remains to be established (Rabinowicz et al, 1995; DeGiorgio et al, 1996; DeGiorgio et al, 1999; Correale et al, 1998).

c. Neuro-imaging

Neuro-imaging findings during and after CPSE were discussed in three patients (Lansberg et al, 1999). Diffusion-weighted MRI (DWI) during CPSE demonstrated marked gyriform cortical hyperintensity throughout the affected hemisphere; T2-weighted MRI and fluid-attenuated inversion recovery images (FLAIR) showed cortical hyperintensity in the abnormal regions seen on DWI. The CT-Scan during CPSE demonstrated new regions of hypo-attenuation in the affected hemisphere. During CPSE leptomeningeal enhancement on post-contrast MRI was present, which may reflect alteration of the blood-brain-barrier; hyper-perfusion during CPSE in response to the elevated metabolic demands was detected with MRA, which demonstrated

increased blood flow through cerebral vessels on the affected hemisphere. Both findings disappeared on follow-up MRI. The lesions demonstrated with DWI, T2-MRI and CT-scan did not respect vascular territories and resolved on follow-up imaging, although some brain injury in two patients was demonstrated. This became apparent as enlargement of the lateral ventricle and sulci on the affected side (Lansberg et al, 1999).
Corresponding MRI findings in patients with primary or secondary brain tumours should encourage EEG investigation to exclude NCSE (Hormigo et al, 2004).

In conclusion it is obvious that clinical evidence for morbidity caused by the epileptic discharges themselves in CPSE is scarce, in relation to its relative high incidence.

Some case reports and the results of modern neuro-imaging technics demonstrate that neurological morbidity may occur after CPSE, caused by the epileptic discharges themselves. The incidence of this problem is probably low. Is the small risk of cognitive sequelae in CPSE worth the risk of intravenous AED morbidity? Prospective studies are needed to answer this question, with better-defined and stratified patient populations.

3.5.3 Simple Partial Status Epilepticus

3.5.3.1 Introduction

Simple Partial Status Epilepticus (SPSE) is characterized by partial seizures without impairment of consciousness, without secondary generalization, and with preserved neuro-vegetative regulation (Gastaut, 1983). Partial seizures with preserved consciousness are called SPSE when continuous clinical and electroencephalographic seizures are present for at least 30 minutes (Delgado-Escueta and Treiman, 1987). The clinical expression depends on the region of the brain where the seizures originate, so various possibilities exist. The most frequent occurring type of SPSE is somato-motor, other types are e.g. aphasic and somato-sensory.

3.5.3.2. Somato-motor SPSE

In general neurological practice two groups of patients with somato-motor SPSE are encountered; both types are in a high percentage caused by a symptomatic brain lesion, but may also occur in patients known with a history of previous epilepsy:

1. Patients with frequently repeated typical somato-motor seizures with or without Jacksonian march and with more or less pronounced EEG discharges in the Rolandic region. Marked vegetative signs are absent (somato-motor SPSE s.s.). In somato-motor SPSE s.s. the seizures consist of local muscular contractions with or without Jacksonian march, not progressing to tonic-clonic seizures, and are so frequently repeated that between the seizures the relaxation of the involved muscles is hardly present. The march follows somato-topic organisation of the motor cortex. The parts of the body involved most in somato-motor SPSE, especially when Jacksonian marches are present, are the face, the eyes and the arms. Without a march clonic jerks are seen most in the thumb, the big toe, lips or eye-lids (Delgado-Escueta and Treiman, 1987). Somato-motor SPSE is the second most common form of SE, after TCSE. Few reviews are present which discuss the various features of this entity, most concern epilepsia partialis continua (EPC). Roger (1974) described 50 patients with partial SE, but only 10 had SPSE without generalisation. Details, such as causes and EEG, of this group were not given.

Another rare type of somato-motor SPSE is *adversive SPSE*, in particular the oculo-clonic form. Patients with oculo-clonic SE have been described with continuous nystagmus and contralateral occipital discharges on the EEG (Gerstle de Pasquet et al, 1991; Kanazawa et al, 1989).

2. Those with persistent myoclonus of cerebral cortical origin in a limited area of the body, present for weeks or months and sometimes in combination with somato-motor or tonic-clonic seizures (Epilepsia Partialis Continua, EPC). Somato-motor SPSE is synonymous with EPC when myoclonic jerks are continuously present in the same body parts engaged by the somato-motor seizures (Delgado-Escueta and Treiman, 1987; Thomas et al, 1977; Schomer, 1993). EPC is characterized by spontaneous regular or irregular clonic twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body, and continuing for hours, days or weeks (Obeso et al, 1985). Juul-Jensen and Denny-Brown (1966) investigated nine patients with EPC who died because of the underlying disease. They suggested a subcortical origin of EPC, but others disagreed (Thomas et al, 1977; Löhler and Peters, 1974; Meienberg and Kabowski, 1977; Shorvon, 1994). Thomas et al (1977) reviewed 32 cases, but included heterogeneous groups of patients with various aetiologies; some patients

were in a comatose state, others were fully conscious and experienced myoclonus for years.

In EPC the myoclonic jerks and the seizures are produced by the same cortical motor area of the brain (Chauvel et al, 1992). Several studies have been able to confirm the constant relationship between myoclonic jerks and focal EEG spikes in the contralateral central area (Wieser et al, 1977; Chauvel et al, 1992). Its nature makes it different from other forms of partial SE, which is due to the peculiar architecture of the motor cortex and of its special, tight afferent-efferent relations, which support the activation of long-loop reflexes. This unique mechanism makes EPC a specific disorder of the motor cortex (Chauvel et al, 1992).

Two types of EPC are discerned (Bancaud et al, 1982; Bancaud, 1985). The first type includes patients of all ages and is caused by a Rolandic lesion of various aetiologies (e.g. brain tumours, CVA). Myoclonias appear later than the somato-motor seizures. The EEG has normal background activities with local spikes or spike-wave activity. Apart from a possible progressive course of the underlying cause, the patient remains stable and does not exhibit a progressive hemiparesis or dementia. The second type of EPC concerns children of 6-10 yrs, with a malignant progressive course of illness. It is characterized by partial motor seizures, which become rapidly associated with myoclonic jerks. Involvement of muscle groups is frequently bilateral and multiple seizure types may be seen. The EEG background deteriorates and shows diffuse slow wave activity. Progressive hemiparesis and dementia become evident with multiple cerebral lesions on the cerebral scan. Prognosis is poor. Evidence for a viral origin of this second type is not conclusive; suggestive are signs of a chronic infectious disease (Dulac et al, 1983) and the results of acyclovir (Ragazzo et al, 1991). The second type of EPC has been described also in adult patients (Gray et al, 1987).

Löhler and Peters (1974) described three cases of EPC of their own and 159 patients from the literature, in the 75 years since the original description of Kojewnikoff in 1895. In the early years, EPC was especially described by Russian authors and linked to viral encephalitis (Russian spring-summer encephalitis). Another group of patients with EPC, presumably caused by a virus, came from Canada. The condition was called Rasmussen's chronic encephalitis but no infective agent has been identified until now (Oguni et al, 1991). Rasmussen's chronic encephalitis and the Russian spring-summer

encephalitis are two distinct entities, both clinically and pathologically; both may result in continuous focal motor seizures. Apart from encephalitis various other causes have been described such as metabolic disturbances, brain tumours, CVA and head trauma. Progressive neurological diseases such as mitochondrial encephalomyopathy with lactic acidosis and stroke-like-episodes (MELAS) should also be considered (Andermann et al, 1986). Other examples of rare causes of EPC are cryptococcal meningitis with EPC of the abdomen (Chalk et al, 1991), EPC following metrizamide cisternography (Shiozawa et al, 1981), cortical dysplasia with very therapy-resistant EPC (Desbiens et al, 1993; Nakken et al, 2005), Sjögren syndrome (Bansal et al, 1987), EPC associated with non-ketotic hyperglycaemia (Singh and Strobos, 1980).

In a cortex biopsy of a case with EPC type II, Verhagen et al. (1988) found patchy necrosis in the deeper cortical layers and the cortico-subcortical boundery. Microangiopathy with perivascular lymphocytic cuffing was a striking finding, suggestive of an inflammatory disorder.

Age distribution shows two peaks, one around twenty and one around sixty years. There is no gender preference.

Clinically myoclonic jerks in EPC are especially present in the face and in the arms. When present in extremities, distal involvement is more frequent than more proximal. The frequency of the myoclonus is in most cases 60-90/min. with varying amplitude. They may be rhythmic or arrythmic and are in most cases (77%) continuously present. In the jerks agonists and antagonists are co-activated unilaterally, and they are by definition spontaneous, but voluntary movement and sensory stimulation can worsen the myoclonus, sleep sometimes lessens them (Thomas et al, 1977; Löhler and Peters, 1974; Biraben and Chauvel, 1997). Neurological examination of the patient shows in most cases abnormalities (94%), especially motor or sensory. Impairment of consciousness is present in few and varies from confusion or drowsiness to stupor and coma. In cases with severe impairment of consciousness another type of SE besides EPC may be present. Cases with severe impairment of consciousness (coma) may also include subtle GCSE or myoclonic SE in coma. This is probably the case in several patients from the review of Thomas et al (1977).

The diagnosis of EPC is primary a clinical one. In cases the EEG shows no specific abnormalities, EEG-EMG back-averaging techniques may demonstrate the relation between specific EEG activity and the resulting myoclonus (Hajek et al, 1991; Cowan et al, 1986; Chauvel et al, 1986; Kuroiwa et al, 1985). Apart from the CT-scan and the MRI, SPECT (Tatum et al, 1991; Katz et al, 1990) and PET (Hajek et al, 1991; Cowan et al, 1986) also may demonstrate focal lesions. This may be important with regard to therapy because conventional anti-epileptic drug treatment is not very successful in EPC and in case of a clear focal origin surgical treatment may offer more success in non-progressive cases (type 1 according to Bancaud, 1982).

Caution is needed in cases with focal abnormalities on CT-scan or MRI because in some these abnormalities are temporary, due to edema and hypervascularisation, which disappear after control of seizures (Dillon et al, 1984; Samaritano et al, 1985; Hormigo et al, 2004).

3.5.3.3 Other types of SPSE

Other types beside somatomotor SPSE or EPC have been described (Gastaut, 1983; Stefan, 1990), but mainly in case reports. The scalp EEG is often uncharacteristic; PET and SPECT may provide helpful information. The following types have been described: somatosensory SPSE (Sailer et al, 1991); psychic SPSE (Sailer et al, 1991; Henriksen, 1973); cognitive SPSE (Matsuoka et al, 1986; Regard et al, 1985; Hojo and Fukushima, 1979); vegetative (or autonomic) SPSE (Sailer et al, 1991); visual SPSE (Barry et al, 1985; Oishi et al, 2003); auditory SPSE (Schiffter and Straschill, 1978); olfactory-gustatory SPSE (Wieser et al, 1985). Aphasic SE with *global aphasia* (Wells et al, 1992; Thomas et al, 1991; Jongsma and Vanneste, 1991; Primavera et al, 1988; Dinner et al, 1981), motor aphasia (Jongsma and Vanneste, 1991; Gregory Hamilton and Matthews, 1979 or Wernicke aphasia (Knight and Cooper, 1986).

3.5.3.4 Incidence of SPSE and EPC

SPSE and EPC are rare; an estimation of the incidence has not been provided, contrary to various other types (Shorvon, 1994). Recent epidemiological studies of SE have mentioned incidence numbers of partial SE, but none about EPC. Prospective studies suggest an incidence of SPSE of 3.0 – 9.4 per 100.000 inhabitants (DeLorenzo et al, 1996; Coeytaux et al, 2000;

Knake et al, 2001). Extrapolating these figures to the Netherlands one may expect at least 480 cases every year. These numbers will especially concern partial motor SE (including many cases with EPC); other types of SPSE are less likely to be recognized and reported.

3.5.3.5 Outcome of SPSE

Outcome of SPSE and EPC depends especially upon the underlying cause. Usually the seizures in SPSE are self-limiting, but recurrence is often noted. Many cases with EPC continue to show convulsive movements despite medical therapy; sometimes surgical excision seems to offer the only hope of remission. Emergency treatment of EPC and other types of SPSE, along the same lines as described for GCSE, is usually unnecessary and often ineffective.

Until recently no convincing evidence was present that SPSE can result in secondary neuronal damage in humans. The incidence of SPSE and EPC is, however, low and most cases are symptomatic. It has been proven that in animals not only focal limbic SE, but also extra-temporal focal seizures can cause neuronal damage (Collins and Olney, 1982; Lothman, 1990; Ben-Ari, 1997). Distant neuronal damage produced by seizure spread (especially in the hippocampus) has been observed.

What is the evidence for morbidity because of the epileptic discharges themselves in humans with SPSE?

a. Clinical case-report

A female patient of 44 yrs suffered from partial epilepsy, because of a head injury. A baseline MRI showed focal atrophy left frontal. She developed SPSE, consisting of her habitual seizures every 5-10 minutes, without medical complications, with duration of 5 days. When SPSE stopped, permanent contra-lateral hemi-paresis was present. MRI after SPSE showed no changes. This case-report suggests that prolonged focal ictal activity by itself can produce permanent neurological damage (Borchert and Labar, 1995).

b. Neuro-pathological investigations

Neuro-pathological investigations of human cases with SPSE or EPC without an acute symptomatic cause are hardly available.

A female patient with chronic obstructive pulmonary disease, acute pneumonia and systemic hypoxia showed SPSE involving the right arm and leg during four weeks. She died because of respiratory insufficiency. Neuro-pathological exam showed neuronal damage (of recent origin) confined to the left hemisphere. It was suggested that hypoxia and the increased metabolic demand because of SPSE caused this damage (Knopman et al, 1977).

Other case-reports obviously did not die because of simple partial motor seizures; they showed other features besides focal motor seizures (several medical complications or coma), suggestive of secondary generalisation (Soffer et al, 1986; Leiffer et al, 1991; Fujikawa et al, 2000). That is why these results cannot be included in the discussion about the relation between SPSE and neuronal damage. Neuro-pathological investigations in SPSE, without an acute symptomatic cause and without other complicating features, are not available at this moment.

c. Neuro-imaging

Local or distant neuronal damage (seizure spread) has been observed in some patients with SPSE: contralateral cerebellar atrophy after SPSE (Duncan et al, 1990); neuronal damage in the hippocampus after focal motor SE (Tien and Felsberg, 1995; Meierkord et al, 1997); a gliotic area (left subcortical pre-central gyrus) after right sided partial-motor SE (Placidi et al, 2001); progressive atrophy of the left hippocampus after SPSE characterized by a permanent amnestic state (Adam et al, 2001).

Decreased levels of N-acetyl-aspartate (NAA) indicates neuronal loss or dysfunction; proton MR spectroscopy (MRS) in a patient with SPSE (visual seizures) showed permanent decreased levels of NAA in the occipital region, even after one year, probably caused by the continuous epileptic discharges during SPSE. Fazekas et al (1995) mentioned a corresponding result in a patient with focal motor SE, which persisted after a period of GCSE.

The case-report and the results of modern neuro-imaging techniques in SPSE suggest a relation between continuous local discharges and corresponding local, but also secondary, neuronal damage. The incidence of this complication will probably be low, because aetiology in most cases

of SPSE is acute symptomatic and the incidence of SPSE itself is low too. In an individual case the probably low risk of neuronal damage will have to be balanced against the possible risk of AED morbidity.

3.6 Status Epilepticus in Children

3.6.1 Introduction

The immature brain is more prone to seizures, but less vulnerable to the long term effects of prolonged seizures; protection of the developing brain from seizure induced damage is, however, not absolute (chapter 3.4.3.) Apart from acute neuronal damage, seizures can induce long-lasting, potentially adverse functional changes in the immature brain that may not appear acutely as injury (Sanchez and Jensen, 2001).

Status Epilepticus (SE) in the neonate differs greatly from that in later childhood or adult life, both from the clinical and the electrophysiological points of view. Apart from that, the causes and anatomic-pathological basis are also distinct. The incidence of seizures in the neonate is very high (1,8-5,1 per 1000 live births). It is estimated that about 33% of the neonates with seizures show SE. Outcome in neonates is especially determined by the aetiology (Mizrahi, 1999). Because of these unique features and the fact that we did not include neonates in our study, we will not discuss SE in the neonatal period.

3.6.2 Epidemiology

The problems of case-ascertainment have been discussed in section 3.3. In children SE is often the first epileptic event, reflecting the high incidence of acute aetiologies and febrile status (Aicardi and Chevrie, 1970; Phillips and Shanahan, 1989). The younger the child, the higher the percentage of acute symptomatic causes of SE (Phillips and Shahanan, 1989). In 394 children SE occurred more often in the age group of less than 2 yr (>40%). In these young children an acute symptomatic or febrile cause was present in more than 80%, whereas cryptogenic and remote symptomatic causes were more common in older children. A history of previous seizures or the presence

of previous neurological impairment was more common in older children (Shinnar, 1997). The risk of epilepsy following SE is increased in acute and remote symptomatic cases, but not in idiopathic SE (Gross-Tsur and Shinnar, 1993). Epilepsy following SE is present in 20-32% of the children (Maytal et al, 1989; Erickson and Koivikko, 1997; Novak et al, 1997; Sillanpää et al, 1998). In population-based studies SE was present in 10% (Berg et al, 2004) to 27% (Sillanpää and Shinnar, 2002) of the children with epilepsy. The occurrence of SE did not modify mortality or remission of epilepsy (Sillanpää and Shinnar, 2002)

The highest incidence of SE in childhood is in the neonatal period; the frequency then falls, to reach a plateau after the first 5 years of life. With increasing age convulsive activity will be less fragmentary and electroclinical correlation will improve. Apart from age, an abnormal cerebral development also will influence the clinical and electrophysiological expression.

The incidence in the paediatric population can be estimated at 20-38 per 100.000 (DeLorenzo et al, 1996; Hessdorffer et al, 1998; Coeytaux et al, 2000). The most frequent type of SE was GCSE (DeLorenzo et al, 1996). The incidence in children is higher than in the adult (15-59 years) population, but lower than in the elderly (> 60 years). The incidence in very young children (< 1 year), however, is the highest of all age groups. The Netherlands has a population of 191.000 children of less than 1 year; the total paediatric population is 2.858.000 (CBS, 1998). Based on these numbers one can calculate the number of children, which will have SE: every year at least 570-1086 children. In the age group of less than 1 year this number is 257. The number of children that will die every year because of SE (and/or because of the underlying aetiology) is at least 14-27.

3.6.3 Types of status epilepticus

The most frequently occurring type of GCSE is TCSE. Other types of generalized SE (tonic SE, clonic SE, myoclonic SE) have been described only occasionally because of their relatively rare occurrence (Roger et al, 1972; Roger et al, 1974; Gastaut, 1983; Shorvon, 1994; Othahara and Ohtsuka, 1997).

Table 13: General characteristics of SE in children. Morbidity referred to new neurological problems, including epilepsy

	Aicardi/ Chevrie 1970	Hayakawa 1979	Vigevano 1985	Yager 1985	Dunn 1988	Phillips/ Shanahan 1989	Maytal 1989
Number	239	67	84	52	97	193	193
Type of SE	GCSE	GCSE	GCSE NCSE EPSE	GCSE NCSE EPSE	GCSE	GCSE	GCSE NCSE EPSE
Duration(min)	>60	>60	>30	>30	>30	>30	>30
Age (years)	<15	<15	<13	<18	<14	<18	<15
Previous Epilepsy (%)	23	83	16	35	49	29	32
Causes (%)							
Acute symptomatic	26	16	42	30	15	43	23
Remote symptomatic	21	–	45	36	57	10	29
Idiopathic	52	–	13	32	28	46	48
Febrile	28	–	6	21	16	32	24
Mortality (%)	11	3	6	6	7	6	3
Morbidity(%)	57	24	21	25	19	?	9

3.6.3.1 Tonic-Clonic Status Epilepticus (TCSE)

Tonic-clonic and clonic (hemi-clonic) SE are the most prevalent types of generalized convulsive SE (Aicardi and Chevrie, 1970; Dulac et al, 1985; Vigevano et al, 1985). More than 75% of the children with convulsive SE have an age of three years or less (Aicardi and Chevrie, 1970; Fuyiwara et al,

1979; Hayakawa et al, 1979). The greater part (50 - 75%) never had seizures before (Aicardi and Chevrie, 1970; Fuyiwara et al, 1979; Hayakawa et al, 1979; Yager, 1988). Except for the studies of Aicardi and Hayakawa neonates (age less than 28 days) were excluded in most studies (Aicardi and Chevrie, 1970; Hayakawa et al, 1979). The types of SE were limited to convulsive SE except for the studies of Vigevano et al (1985), Yager et al (1985) and Maytal et al (1989), who included cases with non-convulsive SE (NCSE) too (table 13). Three other reviews concerning SE in children are rather different from the rest; they concern children of 28days- 1year (Cavazzuti et al, 1984; Aubourg et al, 1985) or 28days - 2 years of age (Dulac et al, 1985). These studies in very young children stressed the high incidence of acute symptomatic causes of SE in this age group. Mortality was strikingly low in the study of Cavazzuti et al (1984), whereas mortality in the group of Dulac et al (1985) was high in comparison to the studies mentioned in table 13, concerning children of all age groups and to the study of Morton et al (1998) in children aged less than 1 year.

The acute symptomatic group consists of central nervous system infections, metabolic problems, anoxia and head trauma (DeLorenzo et al, 1992; Dulac et al, 1985; Vigevano et al, 1985; Cavazzuti et al, 1984; Aicardi and Chevrie, 1970). The prospective study in Virginia (DeLorenzo et al, 1996) reported the following causes of SE in children: systemic infections (52%), low AED (21%), CVA (10%), remote symptomatic causes (38%), hypoxia (5%), metabolic (7%), CNS infection (2%), idiopathic (5%). Mortality was only present in cases with systemic infections (5% of this group). Low AED levels as a cause of SE in children may be not so frequent as presumed; in a group of 51 children with epilepsy and SE in only 9 (18%) all levels of AED were sub-therapeutic (Maytal et al, 1996). With respect to the pathophysiology, the medical complications and of neuropathology in TCSE we refer to chapter 3.4.

3.6.3.2 Febrile status epilepticus (FSE)

FSE is one of the commonest forms of convulsive SE in young children; most are younger than 13 months. FSE occurs more often in children with pre-existing neurological or developmental problems. Febrile seizures occur in 2-5% of the children; 5% of these have FSE of 30 min duration, 0,5% of 60min duration (Hauser, 1990). FSE should be distinguished from acute symptomatic SE with fever, such as in encephalitis or meningitis.

The seizures in FSE are clonic or tonic-clonic and are often focal or unilateral. FSE can be followed by a Todd's paresis or occasionally by permanent neurological deficit. The risk for subsequent febrile or afebrile seizures is increased in neurologically abnormal children with FSE; this is not the case in normal children (Maytal et al, 1990).

Until recently, the outcome of FSE appeared to be poor (Aicardi and Chevrie, 1970; Aicardi and Chevrie, 1983). Permanent hemiplegia or hemiparesis, mental retardation and epilepsy as a result of prolonged FSE had been described in a high number of patients; duration appeared a critical factor (Aicardi et al, 1969; Roger et al, 1972). More recent studies have reported a far better outcome; post-convulsive hemiplegia in FSE appeared rare, which is difficult to explain solely by improved therapy. The conflicting data were due to patient selection bias.

In a follow-up study in a cohort of 14676 neonates 398 (2,7%) had at least one febrile seizure (FS). The risk of later afebrile seizures was much greater in children with lengthy febrile seizures (21%) than in children with febrile seizures lasting less than 30 minutes (3,4%). This study (Verity et al, 1993) also mentioned cognitive deterioration after lengthy febrile seizures in 2 out of 37 children (morbidity 8%). The author discussed this problem in a review about SE associated with fever and, apart from one atypical case, found no evidence of poor intellectual outcome in those who had been normal before the lengthy attacks (Verity, 1997). Cognitive investigations did not show deterioration in children with FSE of 1 hour or more duration (Nelson and Ellenberg, 1976) or with FS of long duration (Ellenberg and Nelson, 1978) or in children with recurrent or prolonged episodes of FS (Verity et al, 1998). Children with prolonged FS (>20min) did worse in nonverbal tests in comparison to single FS and controls. Children with multiple recurrences of FS performed poorer in all tests (Kolfen et al, 1998). A prospective study from a population survey of 4340 live-birth newborns in Taiwan reported that complex or recurring FS were no risk factors for working memory deficits (Chang et al, 2001).

Esch et al (1996) mentioned 24% neurological sequelae after FSE. This study was retrospective; it concerned 57 children with a first episode of FSE in 10 years, admitted to a University Hospital. None had previous epilepsy or a neurologically abnormality. In 9 speech defects were detected, in 3 serious neurological sequelae (psychomotor, epilepsy). FSE might have been

the first presentation of epilepsy in these 3 cases. The neurological sequelae were obvious directly after FSE in 5 children, but only much later in 7 cases (4-14 months after FSE). This study provided important information about long-term follow-up with respect to outcome. A prospective study during 12 years reported the results of FSE in 180 children, age 1 month-10yrs (Shinnar et al, 2001). The results were compared to a group of 244 children with FS (168) and complex partial seizures (76). Outcome in this study was evaluated at 30 days; no morbidity or mortality was present. Considering the results of the study of Esch et al (1996) morbidity during longer follow-up cannot be excluded, although the prospective population-based studies did not provide evidence for this assumption (Verity et al, 1998; Chang et al, 2001).

FSE in children has an overall good outcome in most cases; neuro-imaging has proven that in some cases neuronal damage may occur because of the prolonged seizures themselves (VanLandingham et al, 1998). Pre-existing alteration of medial temporal lobe structures may be important in this respect (Fernandez et al, 1998; Scott et al, 2003). The risk of subsequent epilepsy is increased in cases of lengthy FS, compared to simple FS (Maher and McLachlan, 1995).

3.6.3.3 Non-Convulsive Status Epilepticus (NCSE)

NCSE consists of GNSE and because of the clinical presentation many authors discuss CPSE also as part of NCSE. In most cases NCSE occurs in children with previous epilepsy. The diagnosis of NCSE may be very troublesome because of the lack of familiarity with NCSE, the subtlety of clinical manifestations in some cases and the relatively non-specific nature of the mental changes often seen (Stores et al, 1995; Manning and Rosenbloom, 1987).

The clinical presentation may show an obvious change in behaviour with reduction in activity, slowness, impairment of consciousness, confusion, semi-stupor or pseudo-dementia; sometimes additional ataxia or jerks. In other children the change may be more subtle, such as mild clouding of consciousness, even in the presence of gross EEG abnormality. Clinical features alone are not sufficient to determine the type of NCSE. It is very important to consider the diagnosis of NCSE in children with the above-mentioned clinical features, because therapy may suppress the epileptic

activity and improve quality of life. Therapy may also halt further mental deterioration.

GNSE includes typical ASE and atypical ASE.GNSE may present severe diagnostic problems, especially in mentally retarded patients. In mentally retarded patients with epilepsy, such as children with West or Lennox-Gastaut syndrome, atypical ASE is the most frequently occurring type of GNSE. Other types of SE in these children are TSE, TCSE and MSE.

Atypical ASE

The clinical presentation of GNSE in mentally retarded children is diverse and sometimes very subtle. Essential is a change in behaviour and/or awareness, in combination with ataxia, dysarthria, drooling, myoclonic jerks or twitching and sleep disturbances. EEG investigation is necessary and may show several epileptic EEG patterns: multifocal spikes and spike-waves, diffuse spike and slow waves or poly-spike and slow waves. According to some authors (Dravet et al, 1985; Beaumanoir et al, 1988), GNSE in patients with Lennox-Gastaut syndrome (LGS) has no influence on outcome in comparison to patients without GNSE. Several other studies, however, have described children with mental deterioration after one or more periods of GNSE (Moe, 1971; Doose and Volzke, 1979; Doose, 1983; Manning, 1987; Stores et al, 1995). From their papers however a possible already present pathological process can not be excluded. A recent study in patients with LGS reported that the presence of NCSE in LGS with respect to mental outcome is important (Hoffmann-Riem et al, 2000).

Therapy of atypical ASE is often without effect. Benzodiazepines (BDZ) are only helpfull in some cases; an increase of tonic seizures because of BDZ has been reported (Livingston and Brown, 1987).

Typical ASE

Typical ASE is relatively rare in children. Most are already known to suffer from idiopathic generalized epilepsy with absences and/or generalized tonic-clonic seizures, without any neurological impairment. A typical 3 Hz pattern may be present, but other more irregular patterns are no exception. Most patients are slow, drowsy, show some automatisms or myoclonic jerks. Consciousness may vary from a slightly delayed respons to complete lethargy. Benzodiazepines are successfull in most cases. Precipitating factors include

infections (mostly respiratory), medication problems and stress; in rare cases it is provoked by eye-closure (Aguglia et al, 1985). Duration does not exceed 24 hours in most cases. Cognitive deterioration after typical absence SE in children has not been established.

NCSE in patients with coma without overt clinical seizure signs

In 2 children with coma but without any overt clinical seizure signs, NCSE had been diagnosed. No difference was present in outcome or causes between cases with or without NCSE (Towne et al, 2000).

Complex partial status epilepticus (CPSE)

CPSE in children is recognized by impairment of consciousness, emotional or behavioural problems, lack of response to familiar persons, lip smacking, picking at nearby objects and focal clonic activity. EEG investigation is necessary, in order to distinguish it from ASE and psychiatric problems. Unresponsiveness and brief head nodding seizures may characterize NCSE in children with partial epilepsy, resembling atypical ASE (Ohtsuka et al, 1999). CPSE may also occur in infants (McBride et al, 1981). CPSE in children has not been described often; in 8 studies 18 children with CPSE have been described, all with EEG confirmation (Mayeux and Lueders, 1978; McBride et al, 1981; Balenger et al, 1983; Shalev and Amir, 1983; Mikati et al, 1985; Fukunishi et al, 1988; Ogunyemi et al, 1988; Wakai et al, 1995). This group of 18 children from different studies had an age from 15 months to 13 years; duration in most cases (13) varied from 30 min. to 4 hours, 6 children had a duration of more than 7 hours. Two of them had a very long CPSE (one child of 2 days, the other of more than 60 days). Previous epilepsy was present in 10 cases, previous mental retardation in 10. The recurrent type was the most prevalent (10 cases). In most children the cause remained unknown (9); other causes were fever (3), head trauma (1) and problems with AED (2). One child developed CPSE after removal of a craniopharingeoma. The focus of CPSE was the temporal lobe in most cases, three cases showed an occipital origin, one child a frontal. Outcome in the total group of 19 children was good in 14, unknown in 2, one child showed language delay. In 2 children without previous epilepsy, unprovoked seizures recurred after CPSE. Epilepsy may have been started with CPSE in these cases, not caused by CPSE. The case with language delay after CPSE concerned a child

of 5 years, without previous epilepsy or mental retardation. The cause of CPSE remained unknown. Duration of CPSE was 3 hours, the focus was left temporal. A relation between morbidity and CPSE from left temporal, although not considered, might have been possible; other causes were excluded (Shalev and Amir, 1983).

Apart from complex partial SE, generalized NCSE should be distinguished from an acute confusional state (Amit, 1988), from prolonged postictal encephalopathy (Biton et al, 1990) and acute confusional migraine (Gascon and Barlow, 1970).

3.6.3.4 Simple Partial Status Epilepticus (SPSE)

Simple partial SE is rare in children and is in most cases (75%) somatomotor in expression. Consciousness is not impaired. EPC is mainly limited to already neurologically impaired children (Bancaud et al, 1982). Two types of EPC are discerned (Bancaud et al, 1982; Bancaud, 1985). Progressive unilateral encephalopathy of childhood (Rasmussen's syndrome) is often accompanied by EPC; early hemispherectomy should be considered (Vining et al, 1993). However, the ultimate outcome can be limited by the progressive nature of the underlying cerebral disease. Other types of SPSE in children are rarely reported.

3.6.4 Outcome of convulsive SE

The outcome of convulsive SE is especially determined by its cause. Outcome in children is better than in adults and the elderly (DeLorenzo et al, 1996). In all age groups the underlying cause is the main factor that determines outcome. The particular properties of the developing brain, especially the neuronal plasticity, are important with respect to the more favourable outcome in children.

Other factors of importance are:

1. Age (Aicardi and Chevrie, 1970; Dulac et al, 1985; Maytal et al, 1989; Phillips and Shanahan, 1989). Both Maytal et al (1989) and Phillips and Shanahan (1989) considered this a reflection of the greater incidence of acute neurological disease in the younger age groups. Mortality in children less than 1 year is higher (13,2%) than in children of all age groups (Morton et al, 1998).

2. Duration (Erikkson et al, 1997; DeLorenzo et al, 1992; Yager, 1988; Dunn, 1988; Aicardi and Chevrie, 1970). Maytal et al (1989) is the only one who mentions duration as a significant contributor with respect to outcome of SE in the acute symptomatic group only. Duration of SE in relation to outcome appeared less important in the prospective study in Virginia. In children with prolonged seizures (10-25 min) mortality was absent, whereas mortality in SE was 4%. The difference was, however, not significant. In adults, especially in the elderly, duration was significantly related to outcome, irrespective of aetiology (DeLorenzo et al, 1999)
3. In adults the continuous type of SE is negatively correlated to mortality; in children this is not the case (Waterhouse et al, 1999).
4. Outcome is not related to sex, peripheral WBC count, serum glucose, arterial pH or CSF WBC count in children (Dunn, 1988).

Total mortality in 5 studies (table 13) is 5,8% and morbidity 22,7%; acute symptomatic causes are present in 84% and 55% respectively (Vigevano et al, 1985; Yager, 1988; Phillips and Shanahan, 1989; Maytal et al, 1989; Dunn, 1988). Mortality appears to decline since 1970. Mortality of only 2,5% has been reported by DeLorenzo (1996). However, one has to consider differences in the definition of SE, the time course between SE and death or differences in periods after which new neurological signs are depicted. The time course in the study of Aicardi and Chevrie (1970) between SE and death was 1 year, in Maytal et al (1989) 3 months and in another study 2 years (Dulac et al, 1985). Vigevano described new neurological signs after a period varying from 6 months to 7 years after SE (Vigevano et al, 1985). With differences like these it is hard to compare the results. With respect to outcome in SE it is very important to distinguish outcome because of the underlying cause or because of the longstanding seizure activity itself. It is also difficult to distinguish mortality related to the epileptic discharges from the effect of the medical complications.

What results are known from studies that have investigated neuronal damage because of SE itself?

a. Case reports

1. One of our patients, a boy of six years old and normal development, never showed seizures until 2 days after the start of headache and fever.

He had convulsive SE during a stay at the home of his grandparents. The general practitioner prescribed paracetamol because of the fever. After 7 hours of convulsive SE he was transferred to a near-by academic hospital, still in SE, confirmed by the EEG. Respiratory insufficiency was present at the presentation. Thiopentone was necessary with a partial result; midazolam was successful in the remainder focal seizures. A cause could not be found, despite extensive investigations, including MRI. He was admitted half a year later to an epilepsy centre because of refractory epilepsy, cognitive decline and behaviour problems. A second MRI was normal; his IQ was only 60 with global deterioration. The EEG showed generalized slow activity (4-6Hz). His seizures reacted favourable to the combination of valproate and lamotrigin. At the age of 11 years no changes were reported with respect to cognitive functioning.
Conclusion: global cognitive decline because of inadequately treated GCSE of at least 7 hours duration.

2. A child of 5 years developed partial SE of 5 days duration, followed by GCSE during 5 days. A Ct-scan made 24 hours before the start of SE, because of a first partial seizure was normal. The child developed an acquired opercular syndrome (anarthria, dysphagia, difficulties with chewing, bilateral facial weakness, drooling), neuro-imaging during follow-up (Ct-scan at age 6, MRI at age 16) showed bilateral parietal brain lesions. This case study suggests a relation between brain lesions and SE itself (Pascual–Castrovejo et al, 1999).
3. A boy, 3 yrs, with an uncomplicated medical history, developed generalized convulsive SE with duration of 6 weeks. During SE no medical complications occurred. He died because of sepsis. During SE MRI was performed several times. The first MRI showed no abnormalities. At day 16 the MRI showed T2 hyperintensities in both hippocampi; at day 27 this was seen too, but also in both amygdala and fornices. He died at day 44. Pathological examination showed neuron loss and gliosis in both hippocampi, especially in CA1, CA3 and CA4 and in the amygdala on the right and in the middle layers of the cerebral cortex (Stafstrom et al, 1996).

b. Retrospective and prospective studies of groups of children

Aicardi (1986): from the original group of 239 children with SE, 118 were evaluated in the acute phase and followed for 1 year or more. This retrospective

study is difficult to comment: 142 were seen during or immediately following SE, 97 were examined weeks to years after SE. The authors did not specify the results with regard to these two groups. Mortality some years after SE is hard to attribute to SE itself; this study, however, attributes half of 17 deaths occurring long after SE to SE itself. The 10 cases that died during their SE are not specified whether they were seen in the acute phase or not. Morbidity and mortality related to SE are hard to calculate for this reason. Morbidity because of SE was hard to establish; the results in the cryptogenic group are worthwhile in this respect: 25% in this group had mental retardation and/or neurological deficit, which was not present before SE.

Several other reviews about SE in children have reported outcome related to SE itself (Dulac et al, 1985; Vigevano et al, 1985; Yager, 1988; Dunn, 1988; Maytal et al, 1989; Phillips and Shanahan, 1989; Erikkson and Koivikko, 1997; Shinnar et al, 2001). Four studies were retrospective (Vigevano et al, 1985; Maytal et al, 1989; Phillips and Shanahan, 1989; Erikkson and Koivikko, 1997). Mortality because of SE was low: 0-2%. Morbidity varied from 0-9%. Morbidity (motor dysfunction, visual field deficits, cognitive regression) did not include epilepsy following SE (Dulac et al, 1985; Dunn, 1988; Yager, 1988; Maytal et al, 1989; Erikkson and Koivikko, 1997). In the retrospective study of Erikkson and Koivikko (1997) major neurological sequela (hemiparesis) that might have been attributed to SE, were present in 1 child with FSE (1,5%). The text however, did also mention minor to moderate neurological sequelae (cognitive and/or behavioral problems, motor deficit) present in 4 children with idiopathic or febrile SE and increased disability in one child with FSE. Total morbidity attributed to SE can thus be calculated at 7,7% and not 1,5%. Epilepsy following idiopathic or febrile SE was present in 7 children; SE might be considered as the initial seizure in the evolution of epilepsy, rather than epilepsy being secondary to SE.

c. Neuropathology

Neuropathological studies of children who died during or shortly after SE have shown acute changes in the hippocampus, cerebellum, the cerebral cortex and thalamus. The changes were more striking than in adult patients (Scholz, 1951; Meyer, 1955; Small and Woolf, 1957; Norman, 1964; Radermecker, 1967; Corsellis and Bruton, 1983; Tien et al, 1995; Stafstrom et al, 1996).

d. Neuro-imaging studies

Pneumo-encephalography in 17 of 19 children with various types of SE showed significant degrees of ventricular dilatation, which appeared during follow-up, resulting from atrophy, not because of pre-existing hydrocephalus (Aicardi, 1983; Aicardi, 1969).

A Ct-scan study in 20 children directly after SE showed local edema in 7 cases corresponding to the epileptic focus; a control scan several weeks later showed local atrophy at that spot, suggesting neuronal damage (Gastaut, 1977).

In children (Stafstrom et al, 1996; Tien and Felsberg, 1995; VanLandingham et al, 1998; Herrgard et al, 1999; Lansberg et al, 1999) follow-up MRI-studies have shown that longstanding epileptic discharges can result in neuronal damage, especially in the hippocampus. Several types of SE have been mentioned: GCSE (Stafstrom et al, 1996; Tien and Felsberg, 1995), CPSE (Lansberg et al, 1999) and FSE (VanLandingham et al, 1998; Herrgard et al, 1999). These MRI studies have provided evidence that neurological damage may be caused by continuous epileptic discharges in both GCSE (Stafstrom et al, 1996; Tien and Felsberg, 1995) and CPSE (Lansberg et al, 1999). Recent studies of GCSE in children showed temporary edema in the hippocampus in febrile SE, but not in non-febrile SE (Scott et al, 2002; Scott et al, 2003). During follow-up the volume declined, but it remained undetermined whether this was caused by damage or whether it concerned a pre-existent small hippocampus.

e. Neuron-Specific Enolase (NSE)

Little information is present about NSE in children with SE. No relation was present between duration of seizures and the levels of NSE. In the partial seizure group, but not in the generalized, cerebrospinal fluid (CSF) levels of NSE showed a strong correlation with duration, the same goes for CSF/serum ratio of NSE (Tanabe et al, 2001). A prospective study in 25 previously healthy children with their first SE reported normal CSF-NSE values in all; increased serum-NSE seemed to be related with long SE, but both seizure and neuro-developmental prognosis seemed to be good (Herrgård et al, 2001).

Several case-reports have shown that SE itself may be very deleterious to children. Especially MRI studies have been able to show that neurological

damage may be caused by the discharges themselves. NSE-levels in children appear not to be useful as a marker for outcome.

3.7 Cognitive deterioration in Children and Electrical Status Epilepticus during Slow Sleep

3.7.1 Introduction

Electrical Status Epilepticus during Sleep (ESES) consists of sleep-induced paroxysmal EEG activity, lasting several months or years, which may appear continuously or discontinuously during sleep and is usually diffuse bilateral. ESES is typically of the developmental age, appearing between the age of 3 and 14 years. The paroxysmal activity may also be present during wakefulness, usually in the form of sporadic generalized or focal abnormalities. These cases have apparent clinical manifestations, such as typical or atypical absences, myoclonic or atonic seizures. The most typical paroxysmal discharges of the EEG during sleep are spike-wave (SW) complexes with a frequency of 1.5-3.5 Hz. ESES can develop in several childhood epileptic conditions, but finds its more peculiar expression in some nosological forms, recognized in the classification of the International League against Epilepsy (ILAE). The better-defined syndromes are Continuous Spikes and Waves during Sleep (CSWS) and acquired aphasia or Landau-Kleffner syndrome (LKS). ESES may also be present in Benign Childhood Epilepsy with Centro-Temporal Spikes (BCECT).

CSWS was first described by Patry et al (1971) as subclinical “electrical status epilepticus” induced by sleep in children. They described six children with epilepsy, who showed cognitive regression and whose EEG during sleep showed a pattern of continuous electrical status epilepticus. Later, Tassinari et al (1977) used the term “electrical status epilepticus during sleep” in children or ESES. In 1983 this acronym was replaced by CSWS (continuous spikes and waves during sleep).

Landau-Kleffner Syndrome (LKS) was first described in 1957 in six children (Landau and Kleffner, 1957). LKS, or acquired epileptic aphasia, is characterised in children with epilepsy by verbal auditory agnosia, quickly followed by a regression of spontaneous speech, behavioural disorders and

an EEG during sleep that is similar in many ways to that of CSWS. In 1989 both CSWS and LKS were included in the International Classification of Epilepsies and Epileptic Syndromes of the ILAE.

Epilepsy and epileptiform activity can cause cognitive and behavioural disorders. Studies of this relationship have revealed a more or less direct time link between cognitive disturbances and the diffuse or focal epileptiform abnormalities (Aldenkamp and Arends, 2004). Even (very) brief discharges of a few seconds, without clearly perceptible clinical symptoms, can result in cognitive retardation (Aarts et al, 1984). In CSWS, given the nocturnal epileptic abnormalities, this direct time link between epileptiform abnormality and cognitive functioning is not clear. There are however several indications that a relationship does exist between continuous nocturnal discharges and a regression in cognitive functioning, or behavioural problems (Billard et al, 1990; Marescaux et al, 1990; Roulet et al, 1991; Jayakar and Seshia, 1991; Roulet Perez et al, 1993; Morrell, 1995; Rouselle and Revol, 1995). When evaluating the scientific research into the effects of CSWS on behaviour and on cognitive development we are faced with a number of methodological problems. Firstly, the clinical phenomenology is still insufficiently clearly defined. Secondly, children with CSWS are only sporadically neuropsychologically examined before onset of the syndrome, which makes pronouncements about an eventual regression problematic. Finally, there are major test-psychological differences. Very often only the intellectual level is examined and not the other cognitive aspects, such as language functions. There is also insufficient conformity in the test material employed. Despite these methodological problems, a syndrome description does seem to be possible (Billard et al, 1990; Jayakar and Seshia, 1991; Rouselle and Revol, 1995; Smith, 1997).

Rouselle and Revol (1995) discussed the results of 209 children with ESES and distinguished 4 groups. The degree of epileptic activity during sleep was expressed in an index, which is determined by the total duration of the continuous epileptic activity in relation to the total non-REM sleep duration (spike-wave-index).

1. Children (35) with epilepsy and a normal initial neurological state, without any cognitive deterioration, despite the occurrence of continuous epileptic activity during sleep with an average spike-wave-index of 71%. The main electrical focus showed rolandic topography.

2. Children (33) who developed language deterioration, in 28 corresponding to LKS. The average spike-wave-index was 76%, the main electrical focus was temporal.
3. Children (99) with an initial normal neurological state who developed global cognitive deterioration and severe epilepsy. The average spike-wave-index was 80%, frontal regions were the main focus of paroxysmal abnormalities.
4. Children (42) with focal or diffuse brain lesions who showed global deterioration, with an average spike-wave-index of 80% and a frontal main focus. This group has been described the least accurately and is mostly included in the third group.

The first group has been described by Aicardi and Chevrie (1982) and reviewed by Panayiotopoulos (1999) as atypical benign partial epilepsy of childhood.

Children from the second group have been described as Landau-Kleffner sydrome, children from the third and fourth group as CSWS. In this review the term ESES will be used only to make clear the presence of an electrical status epilepticus during sleep, which may be present in several syndromes with different clinical presentations.

3.7.2 Children with global deterioration, behavioural problems and continuous epileptic activity during slow sleep: CSWS (Billard et al, 1990; Jayakar and Seshia, 1991; Tassinari et al, 1992; Bureau, 1995; Rouselle and Revol, 1995; Smith, 1997; Veggiotti et al, 1999)

Continuous spikes and waves during slow sleep (CSWS) is an age related childhood syndrome characterized by the triad of (1) continuous spikes and waves during slow sleep, (2) seizures, and (3) cognitive decline. In a small number of children, however, seizures never occur.

The incidence and prevalence of CSWS is unknown. A Japanese study found a CSWS pattern in 0.5% of the children with epilepsy studied (Morikawa et al, 1989). A family history of epilepsy is uncommon. It occurs more often in boys than in girls. In 20% to 30% of patients there is evidence of pre-existent brain damage, caused for example by meningitis or a birth trauma. In 30% of patients the CT-scan or MRI shows abnormalities.

Stage I (before discovery of CSWS): The majority (80%) of the children is known with previous partial epilepsy, with mainly partial motor seizures or sometimes unilateral SE. Other seizure types are less often reported and include absences, generalized tonic-clonic seizures or complex partial seizures. The onset of the epilepsy occurs between the 1st and the 10th year, with an average age of 4 to 5 years. Most (75%) have no previous cognitive handicap or behavioural problem. The EEG shows focal or multifocal spike- and slow-wave activity or generalized spike-wave activity. During sleep the epileptic activity increases, sleep patterns and cyclic organisation are preserved.

Stage II (CSWS): The diagnosis CSWS is made around 1 to 2 years after the onset of the epilepsy. The children are then between 4 and 14 years old, with an average age of 8 years. Seizure exacerbation is often present, with various seizure types, including atypical absences, absence SE, atonic or clonic seizures, oro-facial and generalized tonic clonic seizures. Tonic seizures are never noted. Cognitive regression manifests itself in (usually serious) diffuse and/or specific deterioration, primarily of language functions but also of temporo-spatial orientation and memory. Behavioural problems are present with concentration disorders, hyperkinesia, aggression and inhibition disorders.

The EEG during daytime shows abundant slow spike-wave activity, focal and/or multifocal spike and/or spike-wave activity. The main epileptic focus is often frontal or parieto-occipital. The EEG during sleep shows continuous diffuse bilateral slow spike-wave activity (1½-2 Hz, sometimes 3-5 Hz). Poly-spike-wave activity or bursts of fast rhythmic activity are absent. This pattern only disappears in the REM phase, during which the same focal activity may be seen as in the daytime. The various sleep stages, with the exception of the REM-phase, cannot be distinguished. The spike-wave index ranges from 85-100%. The duration of the nocturnal pattern is not always easy to determine and requires a complete sleep registration. These symptoms persist for anything from a few months to several years (Bureau, 1995). One study mentions an average duration of 18.6 months with complete recovery, and of 22.3 months in children with partial recovery (Dalla Bernadina *et al*, 1989).

Stage III (remission): Around the 12th year the EEG during sleep normalises. In one third of patients the epilepsy persists. In 50% of patients

the cognitive prognosis is unfavourable (Bureau, 1995; Praline et al, 2003). The prognosis is better in patients with a shorter CSWS duration (Dalla Bernadina et al, 1989; Bureau et al, 1990). A link with the severity of the epilepsy has not been proven; nor could the presence or absence of cerebral lesion or the age at which the diagnosis CSWS was made be related to the prognosis (Tassinari et al, 1992).

Treatment results of CSWS

The anti-epileptic drugs valproate and/or benzodiazepines have a positive effect in some cases with CSWS and cognitive regression (Smith, 1997; Yasuhara et al, 1991). Incidental positive results have been reported with corticosteroids, ACTH, ethosuximide, clomipramine and amphetamine (Maresceaux et al, 1990; Billard et al, 1990; Okuyaz et al, 2005). Negative results, or even deterioration, have been reported with carbamazepine, phenytoin, and phenobarbital (Boel and Casaer, 1989; Maresceaux et al, 1990; Veggiotti et al, 1999).

3.7.3 Children with acquired specific cognitive disorders and continuous epileptic activity during sleep

The best-known group is with specific language disorders, the Landau-Kleffner Syndrome (LKS). There are also occasional reports of children with ESES and other specific cognitive disorders, such as dyspraxia and non-verbal learning disorders, specific attention disorders and acquired opercular syndrome (Billard et al, 1994; Motte et al, 1994; Shafrir and Prensky, 1995).

LKS or acquired epileptic aphasia is a severe, partly reversible, age-related childhood clinical syndrome with mainly linguistic decline and neuropsychological abnormalities as the main clinical symptoms. The first description has been reported by Landau and Kleffner (1957) under the name acquired aphasia with convulsive disorder. In the literature about 300 cases have been described. The prevalence of this rare syndrome is not known; one study mentioned a prevalence of 0,2% in a cohort of 440 children with epilepsy (Kramer et al, 1998). A family history of epilepsy is present in 12% of the children with seizures; this is reduced to 5% in cases without seizures. Boys are twice likely to suffer from it than girls.

Seizures occur in three-quarters of the patients, but these are usually infrequent and of good prognosis. Seizure onset is between 4 and 6 years. Seizure types include partial motor and generalized tonic-clonic, other types have been less often described (atypical absences, atonic, complex partial). Isolated or single SE may occur. Subtle seizures have been reported during video-EEG recording and are characterized by isolated clonic deviation of the eyes or subjective behavioural manifestations (Morrell, 1995).

The EEG during daytime is characterized by mainly posterior temporal foci of sharp and slow waves, which are often multifocal and bisynchronous. The EEG during slow sleep shows continuous diffuse spike-wave activity, but with a lower index than in CSWS (average 76%). The main activating focus has been located in the intrasylvian region of the dominant hemisphere (Morrell, 1995; Paetau et al, 1999). The EEG normalises after the age of 15 years.

The neuropsychological dysfunction is specific, namely an acquired aphasia (Landau and Kleffner, 1957; Hirsch et al, 1990; Paquier et al, 1992; Deonna and Roulet, 1995; Smith, 1997). Most of the children are initially normal and achieved developmental milestones at appropriate ages, including speech. The language disorder begins with a regression in language comprehension (verbal auditory agnosia), followed by problems of expression that occasionally result in total mutism. Apart from language regression short-term auditory memory disturbances have been noted (Robinson et al, 2001). If the language disorder begins after the age of nine, the nature of the disorder is more expressive than receptive and the prognosis is more favourable (Gerard et al, 1993). Sometimes the symptoms are confused with autism or deafness. The fluctuating course of LKS with exacerbations and remissions makes any assessment of treatment results problematic. Most (80%) of the children present behavioural disorders, such as hyperactivity and aggression, in which it is not clear to what extent these are secondary to the communication problem. Behaviour disturbance may be associated with the presence of frontal lobe discharges in the awake EEG (Robinson et al, 2001). Diagnostic imaging techniques such as CT-scan or MRI usually show no abnormalities.

Language and other neuropsychological disturbances gradually improve at the same age as the disappearance of EEG epileptiform activity. The prognosis is favourable for 30% of the children; the rest show no or

only partial recovery. Half of the children continue to present serious social problems. The prognosis is worst in children with a very young age of onset and in children with considerable delay in treatment. Sometimes there is a spontaneous recovery, but this does not occur when the clinical picture has been present for more than a year. Language outcome was good in only three of eighteen cases; all had impaired short-term memory at follow-up. No child with duration of the electrical status epilepticus during sleep lasting more than 3 years had normal language outcome (Robinson et al, 2001).

Treatment of LKS

The treatment of seizures in LKS does not present many problems. Treatment is instituted to reduce the epileptiform EEG abnormalities on the assumption that these are responsible for the cognitive and behavioural abnormalities. Valproate, ethosuximide, benzodiazepines and corticosteroids have produced positive results, but not always permanent (De Marco, 1988; Maresceaux et al, 1990; Lerman et al, 1991; Aykut-Bingol et al, 1996; Yalcin et al, 1995). Incidental positive results have been reported with felbamate, nicardipine-nimodipine, sulthiam and intravenous treatment with gamma globulins (Pascual-Castroviejo et al, 1992; Yalcin et al, 1995; Glauser et al, 1995; Fayad et al, 1997; Lagae et al, 1998; Mikati and Saab, 2000). In a group of 18 children with LKS AED had no effect on language or behaviour; corticosteroid therapy was successful in two of nine cases with respect to seizures, behaviour and language (Robinson et al, 2001). Some anti-epileptic drugs appear to have an adverse effect: carbamazepine and phenytoin; phenobarbital had no effect (Maresceaux et al, 1990). Most authors advice to start with valproate, ethosuximide and benzodiazepines, alone or in combination; when this fails corticosteroids are started. Duration of corticosteroid therapy depends on the results and may be months to years, in order to avoid escape (Maresceaux et al, 1990).

Some children with LKS have been successfully treated neurosurgically with multiple subpial transections (Morrell, 1995; Sawhney et al, 1995; Irwin et al, 2001). Morrell (1995) applied this technique to 14 patients with LKS. Several techniques were used to establish the area of primary epileptogenic activity. The Methohexital Suppression Test (MST) and the intracarotid amobarbital test provided information about the driving hemisphere. The origin of the epileptic discharges could be established with dipole mapping

and simultaneous recording of EEG and MEG (magneto-encephalography). The origin appeared to be located on the dorsal surface of the superior temporal gyrus, essentially in the auditory association cortex, which was confirmed by electrocorticography during the MST procedure. MST of this unilateral Sylvian site resulted in disappearance of the epileptiform discharges bilaterally (Morrell, 1995). The intrasylvian location of the pacemaker in LKS has been confirmed by other studies (Paeteau et al, 1999). The 14 children with LKS, who underwent MST by Morrell et al (1995), were subject to a follow-up study (Grote et al, 1999). Eleven children showed significant improvement on measures of receptive or expressive vocabulary. The most obvious difference between children who did and did not show significant improvement was the length of time between surgery and the most recent evaluation. Patients tested 2 or more years after surgery showed significant more improvement than if tested a few months after surgery. Significant improvement did not occur when tested within 6 months after surgery. All children continued to have reduced auditory attention span. The effects of surgery are difficult to disentangle from the natural history of LKS.

MST was also applied to 5 children with LKS with dramatic effects on seizures and behaviour and only minor effects on language (Irwin et al, 2001). Improvement of language occurred in all 5 children, but none to an age-appropriate level. The mean length of the period with ESES was 4.6 years with a range from 3 to 6 years. MST did have an important effect on behaviour, which, according to the authors, justifies the procedure. The timing of surgery in patients with LKS requires further study; intervention within 3 years was suggested.

3.7.4 Pathogeneses of CSWS and LKS

The cause of these age-related syndromes is unclear. It has proved impossible to point to any specific cerebral lesions that could be held responsible for the syndrome in a range of patients. Comprehensive examination of numerous patients has so far yielded inconclusive results. Many researchers consider the prolonged epileptic discharges to be responsible for the specific cognitive problems or overall deterioration. The EEG shows bilateral synchrony arising from an epileptic focus; the initial topography and the duration of the

continuous epileptic activity during slow sleep causes the neuropsychological disorder (Paeteau et al, 1999). It is known that the basal network of the brain develops between the ages of 1 to 8 years. If disturbances take place during this period, this may result in permanent impairment of this network. The number of axons and synapses in this age group is approximately twice as many as in adults. Abundant epileptic activity causes a reinforcing of synaptic contacts that should normally disappear during this period. This causes disturbance of the normal functioning of the area in which this epileptic activity is concentrated. In the case of CSWS this is probably the frontal region, which results in disorders of various higher cognitive and behaviour regulatory functions. In LKS it is the temporal lobe that results in specific language disorders. Over time this dysfunction can spread across a wider area of the brain and thus give rise to other disorders. Because the epileptic activity is bilateral the disturbed function cannot be taken over by the contra-lateral homotopic cortex (Smith, 1997). If the continuous local EEG abnormalities during sleep do not spread but remain local, cognitive disorders are less often described (Galletti et al, 1992).

Bilateral synchrony from an epileptic focus as an important feature of the pathogeneses of CSWS and LKS has been demonstrated by the following results:

a. Intravenous injections of benzodiazepines cause disappearance of the continuous spike-wave series (which indicates, amongst other things, that this is no sleep variation) and emphasise a clear frontal focus in children with global deterioration (Tassinari, 1995; Kobayashi et al, 1988).
b. The autonomous epileptic focus from which the secondary bilateral synchrony arose could be determined by means of methohexital suppression test, intracarotid amytal, EEG dipole mapping, MEG and electrocorticography during MST (Jayakar and Seshia, 1991; Park et al, 1994; Morrell, 1995; Patil and Andrews, 1998; Paeteau et al, 1999).
c. Involvement of the temporal lobe in LKS has been demonstrated by SPECT studies (Guerreiro et al, 1996) and PET studies (Rintahaka et al, 1995; Da Silva et al, 1997). A PET study in CSWS demonstrated a focus right temporo-parietal (Park et al, 1994).

A link between ESES and the cognitive or behaviour disturbances has been demonstrated by the following results:

a. If the ESES pattern on the EEG disappears (under the influence of AED for example) cognitive functioning and behaviour improves (Pelliccia et al, 1989; Maresceaux et al, 1990; Roulet et al, 1991; Yasuhara et al, 1991).
b. The results of multiple subpial transection in LKS (Morrell, 1995; Sawhney et al, 1995; Irwin et al, 2001).

Other researchers argue for a link with a specific cause, such as a tumour or an inflammation. (Perniola et al, 1993; Solomon et al, 1993; De Volder et al, 1994). Pathological anatomical examination of received material has so far revealed nothing specific (Cole et al, 1988; Smith et al, 1992). There is thus sufficient reason to postulate that it is the age at which the syndrome develops, the localisation of maximum epileptic activity and the bilateral spread of the epileptic activity that determine the clinical picture and not a particular aetiology.

An interesting study in 4 children with LKS showed a reduction of 36-51% in the cortical volume of the superior temporal areas, using MRI volumetric analysis. These areas correspond to the auditory association cortex. There was no left or right hemispheric preponderance, but the volume reduction was greater on the side with more epileptiform activity in two children (Takeoda et al, 2004). The focal atrophy may explain why long-term prognosis is often poor. Further research is necessary to answer the essential question whether the atrophy is the cause of LKS or the consequence of excitotoxicity.

3.7.5 Differential diagnosis

Pervasive development disorder and autism: Although children with these disorders may also show epileptic abnormalities on the EEG, there is no cognitive regression and no CSWS. Autistic epileptiform regression (AER) is an exception to this rule. These children often show epileptic abnormalities on the EEG, usually multifocal and over a wider area than in LKS. Multiple subpial transections have proved successful in a number of these children, suggesting a relation between epileptic activity and cognitive regression (Patil and Andrews, 1998).

Lennox-Gastaut Syndrome (LGS): Patients with LGS more often present neurological abnormalities and mental retardation from an early age. These children do have tonic seizures. The EEG during sleep shows an increase of slow spike and wave, but not to the same extent as in CSWS. The EEG during sleep also shows fast discharges, which does not occur in CSWS. *Benign Childhood Epilepsy with Centrotemporal Spikes (BCECT):* On the EEG during sleep this syndrome can show a strong increase in epileptic activity. This is sometimes continuous, but with a lower index than in CSWS. The focus of the EEG activity in BECT lies in the centro-temporal areas. Until recently cognitive disorders were seldom reported in children with BCECT. A few recent studies mention cognitive problems (visual perception, attention and short term memory) and behaviour disturbances in BCECT (Weglage et al, 1997; Croona et al, 1999; Ong and Wyllie, 2000). A relation between cognitive deficits and the frequency of the spikes has been suggested (Weglage et al, 1997). A single cognitive profile was not identified. Children with difficulties at school improved together with improvement of the EEG (Deonna et al, 2000). In two children with *Benign Childhood Epilepsy with Occipital Spikes (CEOP)* continuous occipital spike-wave activity during the day (which disappeared with eye opening) and continuous generalized spike-wave activity during sleep was demonstrated, with a disruption of their epilepsy and behaviour accompanied by overall cognitive regression (Tenembaum et al, 1997).

3.8 Status Epilepticus in Mentally Retarded Patients

3.8.1 Prevalence and incidence of Status Epilepticus (SE) in Mental Retardation (MR)

The prevalence of Mental Retardation (MR) in the general population has been subject of several studies (Roeleveld et al, 1997). The true prevalence rate for mild mental retardation (MMR, IQ 50-70) appeared much more difficult to estimate than for severe mental retardation (SMR, IQ <50). The variation in prevalence rates of MR has been reported also in studies dealing with the occurrence of epilepsy in patients with MR. Life-time history of

epilepsy in MR varies between 14-24%. The variation in overall prevalence rates of epilepsy in MR is partly explained by the use of different definitions for diagnosing epilepsy and by the problem of case ascertainment. The prevalence of epilepsy in MR depends on the age group, the severity of MR and the associations with other neurological disorders. The prevalence of epilepsy in MR at age 10 was 1.9 per 1000, at age 22 years 2.1 per 1000 (Airaksinen et al, 2000). The cumulative incidence of epilepsy in MR was 9, 11, 13 and 15% at age 5, 10, 15 and 22 years, respectively (Goulden et al, 1991). In patients with MMR epilepsy was present in 15 %, in patients with SMR in 45 % (Steffenburg et al, 1996). The prevalence of epilepsy in MMR increases when cerebral palsy is present or a postnatal cause had been established (Aikraksinen et al, 2000).

According to Shorvon (1994) the risk of status epilepticus (SE) in patients with epilepsy and mental retardation is high. Little information about prevalence and incidence of SE in patients with MR is available, however. Some studies mentioned the prevalence of SE in a group of patients with MR:

- In 98 children (6-12 years) with MR and epilepsy SE occurred in 37 patients (37 %), the recurrence rate was 35 %. Convulsive SE was present in 32 patients, non-convulsive in 5. (Steffenburg et al, 1996).
- In population of children and adults with MR and epilepsy the prevalence of convulsive SE was 18.7 % (Forsgren et al, 1990).
- At 22 years of age 12,5 % of patients with MR and partial epilepsy had a history of SE (Airaksinen et al, 2000).

These figures are not very different from those in the total population. Hauser (1990) reported that 20% of patients with epilepsy from the total population would experience an episode of status epilepticus within 5 years of initial diagnosis of epilepsy. In a long term follow-up study of 245 children with epilepsy 32% showed status epilepticus (Sillanpåå et al, 1998). It should be noted, however, that many cases of SE in patients with MR would not be documented. This is especially the case for non-convulsive status epilepticus (NCSE), a diagnosis easily overlooked in patients with MR.

3.8.2 Types of SE in MR

In a retrospective study 39 mentally retarded patients with 86 episodes of SE were gathered in 8 years (Phillips et al, 1996). All were institutionalized developmentally disabled clients admitted to the acute care unit. All were known with previous epilepsy, 17 showed recurrent episodes of SE. The most frequent occurring type was tonic-clonic SE (88%), followed by myoclonic SE (7%), partial motor SE (3%), tonic SE and complex partial SE (1%). Causes or precipitating factors included intercurrent illness (41%), low anti-epileptic drugs levels (17%), idiopathic (38%) and other (3%).

The most occurring type of SE in MR is Tonic-Clonic Status Epilepticus (TCSE). The clinical features and pathophysiology have been described (Shorvon, 1994). Some types of SE occur almost exclusively in MR such as atypical absence SE, tonic SE (TSE) and minor motor SE (Shorvon, 1994). Various syndromes with epilepsy and MR frequently show one or several types of SE. The best-studied type is Lennox-Gastaut-Syndrome (LGS). Patients with LGS have a high incidence of clinical evident SE (Beaumanoir et al, 1988). TSE and atypical absence SE are the most frequently occurring types of SE in LGS. SE could be precipitated by under stimulation or polytherapy. Preceding SE, the patient showed an increase of tonic seizures during sleep, with slowness or tiredness during daytime. An increase of irritability was possible too. Various types of SE could be present; all showed confusion and could be accompanied by hypotonia, myoclonic jerks, tonic or astatic seizures. The EEG showed generalized slow spike-wave activity or diffuse 10 Hz activity followed by slow spike-wave activity. Duration of SE varied from several hours to several weeks. Older patients with LGS also showed generalized convulsive SE. A syndrome with many clinical resemblances to LGS is myoclonic-astatic epilepsy (Doose syndrome). Patients with this syndrome have high incidence of absence SE.

The diagnosis of NCSE in MR may offer serious problems (Shorvon, 1994; Brodtkorp, 1993).

The calculated annual incidence, 100-200 per million, suggests that many cases of NCSE will be overlooked with subsequent consequences for quality of life and cognitive deterioration.

Consciousness in NCSE may vary from a slightly decreased level to stupor. A spectrum of various other signs may be present: agitation, confusion, automatisms, apraxia, regressive behaviour, incontinence, tremor or myoclonic jerks. It is obvious that changes in the clinical presentation of patients with MR should raise the question whether NCSE may be present. EEG investigation should be considered, especially when other clinical features accompany changes in the level of consciousness. EEG investigation is also important to distinguish NCSE from post-ictal confusion or pseudo-SE (Drake et al, 1992) and to establish the type of NCSE, CPSE or atypical ASE. Myoclonic SE (MSE) of long duration occurs in children with severe myoclonic epilepsy and in myoclonic epilepsy with non-progressive encephalopathy. MSE in patients with progressive myoclonic epilepsies has a comparable clinical expression as primary MSE. In these patients MSE may be precipitated or excacerbated by action or startle. Prognosis depends on the underlying cause (e.g. mitochondrial encephalopathy with ragged-red-fibres, Lafora body disease and Unverricht-Lundborg disease), although not in all cases a specific cause can be found. MSE may also be present in patients with symptomatic generalized epilepsy, such as Lennox-Gastaut syndrome (secondary MSE). This type has been reported as minor motor status (Brett, 1966). Secondary MSE is often asymmetrical and shows a variable extent of impairment of consciousness. Variable symmetric and asymmetric myoclonic jerks are seen in the limbs, trunk and eyes. Most children are obtunded and drooling; speech is absent or slurred. Sudden atonia may occur. Walking is unsteady (pseudo-ataxia). The EEG shows multifocal spikes and spike-wave discharges. Treatment is unsuccessful in most cases, and prognosis is poor. The clinical presentation and the results of EEG investigations make it sometimes difficult to distinguish this type of MSE from atypical ASE (Othahara and Ohtsuka, 1997).

3.8.3 Outcome of SE in MR

Outcome of convulsive SE in MR has not been subject of a separate study. Little is known about the causes of convulsive SE in MR. Morbidity in TSE is not known, mortality about 3%. It is not clear, however, whether or not cerebral damage results from Tonic SE. One case showed cognitive deterioration after TSE (Somerville and Bruni, 1983). Outcome of NCSE in MR is not

known. According to some authors (Dravet et al, 1985; Beaumanoir et al, 1988), GNSE in patients with Lennox-Gastaut syndrome has no influence on outcome in comparison to patients without GNSE. Several other studies, however, have described children with mental deterioration after one or more periods of GNSE (Moe, 1971; Doose and Volzke, 1979; Manning, 1987; Stores et al, 1995). From their papers, however, a possible already present pathological process cannot be excluded. A recent study in patients with Lennox-Gastaut syndrome reported that the severity of mental retardation was related to the occurrence of NCSE, odds ratio 25 (Hoffmann-Riem et al, 2000).

3.8.4 Therapy of SE in MR

Therapy of convulsive SE in MR has not been a separate subject of research. Several authors have discussed therapy of NCSE in MR; the results were often disappointing (Shorvon, 1994; Brodtkorp et al, 1993; Beaumanoir et al, 1988; Brett, 1986). The use of ketamine, a NMDA-receptor antagonist, in NCSE may be of value (Mewasingh et al, 2003).

3.8.5 Conclusions

SE in MR has specific characteristics:
- The incompleteness of cerebral development.
- Specific aetiology of MR.
- Some types of SE occur only in MR.
- Some syndromes of epilepsy and MR show a high incidence of SE.
- Results of therapy of some types of SE.

It is concluded that characteristics and incidence numbers of SE in the general population cannot simply be extrapolated to persons with MR.

3.9 Treatment of Generalized Convulsive Status Epilepticus

3.9.1 Introduction

First line drugs, such as benzodiazepines (BDZ) and phenytoin (PHT), are successful in 80% of the cases when therapy is started within 30 minutes after the start of the seizures; when therapy is started after 2 or more hours, first line therapy fails in 60% of the cases (Walton and Treiman, 1988; Lowenstein and Alldredge, 1993). Many authors state that therapy delay contributes to a longer duration (Treiman et al, 1983; Lowenstein et al, 1988). This is also the case for inadequate therapy (Delgado-Escueta and Enrile-Bascal, 1983; Celesia, 1983). Experimental results in animals have stressed the importance of adequate treatment of the medical complications occurring during the course of GCSE (Meldrum et al, 1973; Meldrum et al, 1974; Siesjo and Wieloch, 1986). In these experiments it was shown that early intubation, mechanical ventilation and artificial paralysation (after 1 hr) lessen the degree of hyperthermia and acidosis and prevent muscle necrosis, with less risks of renal failure and cardiac arrhythmias. In human studies the degree of metabolic acidosis did not correlate with outcome, hyperthermia on the other hand, caused a worse outcome (Aminoff and Simon, 1980). Treatment-protocols have been developed; although it is generally agreed that a long duration of SE aggravates outcome, the use of a time-schedule is still limited (Delgado-Escueta and Bajorek, 1982; Treiman, 1989; Working group on SE USA, 1993; Chin et al, 2003; Pellock et al, 2004).

3.9.2 Which drug should be used during the various phases of generalized convulsive status epilepticus?

3.9.2.1 Premonitory stage

Benzodiazepines (BDZ) are the drugs of first choice for treatment in the premonitory stage and in the early phase of SE because of their speed of action and the relative absence of adverse effects. The choice which of the available BDZ should be used for treatment of SE is not based on clear differences with respect to clinical effect, because these differences are not

clearly established (Sorel et al, 1981; Tassinari et al, 1983; Treiman et al, 1983; Leppik et al, 1983; Giang and McBride, 1988; Andermann et al, 1992; Appleton et al, 1995; McCormick, 1999; Qureshi et al, 2002). The choice will be determined by previous experiences, pharmacokinetic parameters and the presence of facilities for resuscitation. During the premonitory stage seizures become increasingly frequent or severe, treatment may prevent the evolution into true SE. Emergency situations require rapid intravenous administration of an appropriate AED; one frequently encounter situations in which adequate venous access is not available (home settings, long-term care facility) or would entail significant time delays, especially in children. In such settings an alternative parenteral route would be desirable. Rectal administration of diazepam (Cereghino et al, 1998; Dreyfuss, 1998), buccal (Scott et al, 1997; Scott et al, 1998; Scott, 1999; Fernando et al, 2000) or subligual midazolam and nasal midazolam (O'Regan et al, 1996; Scheepers et al, 2000; Mahmoudian and Zadeh, 2004) are effective and safe modes of treatment during this stage. Before or during transport to the hospital paramedics may administer intravenous lorazepam or diazepam, with a preference for lorazepam (Lowenstein et al, 1999; Alldredge et al, 2001). When intravenous (i.v.) access is difficult (e.g. small children) midazolam intramuscular (i.m.) may be considered (Chamberlain et al, 1997). The use of i.m. AED in the acute treatment of SE is limited to midazolam, with clinical effects within 2-3 min (Egli and Albani, 1981). One should anticipate respiratory depression after i.m. midazolam. Fos-phenytoin i.m. has a relatively slow onset of action, which limits its use for acute treatment of SE. The i.m. administration of fos-phenytoin in the prehospital situation, before transport to the hospital, appears to be safe and limits therapy delay.

The use of *paraldehyde* (PA) is limited to rectal administration in the pre-hospital phase, as an alternative or sequel to diazepam or in situations where facilities for resuscitation are not available (Browne, 1983).

3.9.2.2 Early status epilepticus (0-30 min)

Once SE has developed, the patient should be admitted to the local hospital, with facilities for resuscitation and EEG monitoring. There is limited information about comparative prospective trials of different anti-epileptic drugs in the early phase of SE.

In a prospective double blind trial 395 adult patients with overt GCSE and 113 with subtle GCSE were randomly assigned to receive intravenous Lorazepam (LZP), Phenobarbital (PB), PHT or Diazepam (DZP) followed by PHT (Treiman et al, 1998). LZP was significantly more effective than PHT in overt GCSE, other comparisons did not show significant differences. Infusion-time is shortest in LZP (4,4min), followed by PB (16,6min), PHT (33min) and DZP+PHT (42min). No significant differences were noted with respect to side effects. When the initial drug fails, little was gained by using other standard AED. One should consider rapid addition of i.v. general anaesthesia if initial treatment fails (Treiman, 1997). The results of this prospective study suggest that LZP is the drug of first choice in the early phase of GCSE with regard to effect, speed of infusion-time and ease of use. It was striking that PB, which enters the brain slowly, was not less effective than LZP. Treatment with DZP should be combined with PHT to avoid recurrence of seizures within 10-20 min. PHT as the only drug in this stage is not recommended because of the slow onset of action and the long infusion-time.

Together with BDZ, *phenytoin* (PHT) is a first-line drug in the treatment of GCSE. The advantage of PHT is its lack of sedative and respiratory depressant effect and the long duration of action. A disadvantage is the delay of onset of action, 10-20 min. In 80% of the patients the effect is present within 20 min (Cloyd et al, 1980). Duration of action after a loading dose is about 24 h or more. Recently fos-phenytoin (fos-PHT), which is watersoluble, has been tested in GCSE (Legarda et al, 1993; Boucher, 1996; Browne, 1996; Wilder, 1996; Pryor, 2001). Fos-PHT is rapidly and completely hydrolysed in the blood by phosphatases and converted to PHT (1,5 mg fos-PHT= 1mg PHT). The dose of fos-PHT (PE) is expressed as the amount of PHT when converted in the body (PE= PHT equivalent). Intramuscular administration is also possible. Conversion-time is 7-15 min intravenous and 30 min intramuscular. Therapeutic levels are reached after 10min (i.v.) and within 30 min after i.m. administration. Local irritation has been rarely reported after i.m. administration (1-7%); 20cc have been tolerated fairly (Pryor, 2001).The advantages of fos-PHT in comparison to PHT are a higher speed of loading, less local irritation after i.v. administration, the possibility of i.m. use and no cardiac rhythm complications (Fischer et al, 2003).

Although penetration of *phenobarbital* (PB) into the brain is relatively slow, clinical effects have been established within minutes (Goldberg and McIntyre, 1983). Blood levels over 20 mg/l are necessary; to abolish all ictal activity, much higher levels (over 70 mg/l) may be necessary (Walton and Treiman, 1989). The drawback of PB is the possible respiratory depression and its very long duration of action. Other adverse effects are sedation and less frequently hypotension. High dose PB therapy, with blood levels over 70 mg/l was successful in children, although response latency was not mentioned and outcome poor (Crawford et al, 1988). A significant shorter median cumulative convulsion duration and a significant shorter median response latency was reported in comparison with DZP and PHT i.v. (Shaner et al, 1988). PB is a highly effective AED with a rapid onset and a prolonged action, with high concentrations in the active epileptic focus.

The use of *lidocaine* in GCSE until now has been limited to cases refractory to other drugs (De Giorgio et al, 1992; Pascual et al, 1992; Aggarwal and Wali, 1993). In patients with respiratory problems or in cases when respiratory support is not possible, lidocaine can be considered (Pascual et al, 1988). If successful, the effect is present within minutes; refractory cases after 1 injection hardly respond to repeat injections or an infusion. When seizures reappear after a first successful injection, infusion may be considered. Because of possible cardiovascular effects, monitoring of ECG and bloodpressure is necessary.

3.9.2.3 Established stage of status epilepticus (30-60 min.)

Patients in this stage of SE carry great risks for medical complications; treatment should occur at the Intensive Care Unit (ICU). Treatment until this stage will have consisted in most cases of BDZ and/or PHT. There are no adequate comparative trials of anti-epileptic drugs (AED) in this stage available. Several possible first-line drugs may be considered: PHT or fos-PHT, PB, MDZ-infusion and valproate (VPA).

MDZ infusion has been successful in both children and adults, also in cases refractory to LZP, PHT or PB (Kumar and Bleck, 1992; Parent and Lowenstein, 1994; Claassen et al, 2001; Ozdemir et al, 2005). Seizure recurrence after control of SE should be anticipated, however (Singhi et al, 2002).

The use of *VPA* i.v. in SE has not been established, but is promising (Giroud et al, 1993; Czapinski, 1995; Seth and Gidal, 2000; Naritoku and Sinka, 2001; Limdi et al, 2005; Pohlmann-Eden et al, 2005). The onset of action has been shown to be more rapid than expected (Giroud and Dumas, 1988; Giroud et al, 1993; Peters and Pohlmann-Eden, 1999; Ueberall et al, 2000; Yu et al, 2003). The use of VPA i.v. appeared safe, also in elderly (Devinsky et al, 1995; Ramsay et al, 1997; Wheless et al, l998; Sinha and Naritoku, 2000). In children VPA i.v. can be safely infused over a 30min period (Alvarez et al, 1999). In elderly VPA showed similar efficacy in SE than PHT, although one should pay attention to possible side effects: trombocytopenia, cardiac arrhytmias, hyperammonemia and liver failure (Wedel et al, 2000). Further research is necessary to establish its place in the treatment protocol.

3.9.2.4 Refractory status epilepticus (after 60-90 min)

When seizures do not respond to one or two treatment regimens and continue 60-90 min after initiation of therapy in the stage of established SE, SE is considered refractory. Full anaesthesia is required, some have advised to start anaesthesia earlier (Treiman, 1997). First line drugs in this stage are thiopental and propofol, both with a considerable potential for adverse events. Adequate comparable trials of suitable drugs are not available. Thiopental may cause severe adverse events, especially during prolonged infusion. In comparison to propofol it showed a significantly longer time to seizure control (Stecker et al, 1998).

The use of *thiopental* in GCSE was described first in 1967 (Brown and Horton, 1967). Various case reports and reviews have appeared since then (Osorio and Reed, 1980; Orlowski et al, 1984; Lowenstein et al, 1988; Ness, 1990). The results of barbiturate coma are variable because of underlying diseases and the duration of GCSE previous to thiopental treatment. Most case reports or reviews concerning barbiturate coma in refractory GCSE describe patients who fail to respond to common first line-drugs such as DZP and/or PHT. A large number of these patients have an acute symptomatic cause of GCSE (Yaffe and Lowenstein, 1993). A unanimously accepted protocol is not present. Characteristics of the EEG such as burst-suppression nor the blood-levels, can be used to predict therapeutic efficacy. A relation between drug-level and EEG, between drug-level and effect and between EEG and effect could not be established (Osorio and Reed,

1989). In patients with EEG-burst-suppression, clinical seizures were still present, whereas in other patients seizures were stopped without burst-suppression. Adjustment has to be based on the presence of clinical seizures and or electrical seizures. Because the duration of bursts and of suppression segments during thiopental treatment are very variable, they cannot be related with the end of SE. One study suggested better results of attaining a flat record in comparison to burst-suppression in patients with SE treated with barbiturate anaesthesia (Krishnamurthy and Drislane, 1999).

Most authors advise thiopental treatment after 1 - 2 h of GCSE, refractory to common first line drugs, and the use of EEG-monitoring (aiming at burst-suppression or an iso-electric-EEG) as a guideline. Duration of thiopental treatment should be limited because of the danger of severe adverse events (hypotension, paralytic ileus, various infections such as sepsis, increase of pCO2) and the lack of evidence that prolonged treatment offers better results. Especially patients with previous respiratory or cardiovascular problems may be poor candidates for barbiturate coma. Apart from the anticonvulsant effects, thiopental may lower intracranial pressure and cerebral metabolic rate of oxygen and glucose (CMR-O2 and CMR-gluc). The drug has a strong tendency to accumulate; recovery times may be very protracted. Treatment with thiopental implies admission at the Intensive Care Unit because of the need for mechanical ventilation, the possible use of vasopressors, a Swan-Ganz-catheter and the treatment of other possible medical complications, either related to the severity of SE and/or to the use of thiopental itself.

Propofol infusion during SE has been described in several patients, refractory to first and/or second line drugs, such as DZP, clonazepam (CZP), PHT, PB, thiopental and chlormethiazole (Yanny and Christmas, 1988;Wood et al, 1988; Thomas and Morgan, 1989; MacKenzie et al, 1990; Kapadia and Grant, 1990; Borgeat et al, 1994; McBurney et al, 1994; Rosetti et al, 2004). Propofol and high dose barbiturates showed comparable results, but the time to seizure control was significantly lower in the propofol group than in the barbiturate patient group (Stecker et al, 1998). In adult patients propofol and MDZ had comparable results in refractory SE (Prasad et al, 2001). In both children and adults propofol may cause metabolic acidosis, progressive myocardial failure, progressive hypoxia and rhabdomyolysis (Hanna and Ramundo, 1998; Cremer et al, 2001). Administration requires intensive

care facilities, including the possibility of mechanical ventilation. Prolonged infusion (> 24 hrs) of both thiopental and propofol should be avoided.

Miscellaneous drugs used after failure of thiopental or propofol include chlormethiazole, etomidate and inhalation anesthetics

Chlormethiazole (CTZ) is a sedative-hypnotic drug with rapid anti-epileptic effects and is freely soluble in water (Laxenaire et al, 1966; Bentley and Mellick, 1975; Lingham et al, 1981). It may be successful in cases refractory to BDZ, PB and thiopental (Nouailhat et al, 1985). Monitoring blood pressure, ECG and EEG is necessary. Haemodynamic monitoring (Swan Ganz) in cases of high doses is needed because of the large volumes of infusion. The possibility of mechanical ventilation should be present. CTZ has never been subjected to a formal comparative study. In most case reports it was used in combination with other drugs. The delay in onset of action may be 1 h, although a more rapid onset of action has been mentioned (5-30 min). Continuous infusion of CTZ is necessary to prevent recurrence of seizures (distribution half time 30 min.).

Etomidate is a short acting non-barbiturate carboxylated imidazole with hypnotic and anticonvulsant effects. Conflicting results are present with regard to treatment of GCSE (Starre, 1980; Yeoman, 1989). On the other hand etomidate may cause involuntary muscle contractions, tremor and hypertonia at induction of sedation. Co-administration of opoids or BDZ is frequently necessary with continuous infusion of etomidate to avoid muscle contractions or even convulsive activity (Grant and Hutchinson, 1983). The use of etomidate in cases of delirium tremens caused myoclonia and generalized tonic-clonic seizures in 5 of 7 patients with EEG confirmation of the epileptic nature (Nickel and Schmickaly, 1985).

The use of *inhalation anaesthetics* in GCSE is rare. The drawbacks of *halothane* are serious haemodynamic adverse events and potential hepatotoxicity. *Isoflurane* (0.5 - 2%) may offer a possibility in refractory cases (Kofke et al, 1989; Mirsattari et al, 2004). *Althesin* is an i.v. anesthetic consisting of two steroid derivates (alphaxalon, alphadolone). Only 2 studies report success in GCSE (Munari et al, 1979).

3.9.3 Treatment according to protocol

Treatment of SE according to protocol has been increasingly promoted (Delgado-Escuate and Bajorek, 1982; Leppik, 1986; Treiman, 1989; Working group on SE U.S.A, 1993; Advanced Life Support Group, 1997; The Status Epilepticus Working Party, 2000). This does not always result however, in clinical application of treatment of SE according to protocol (Martland et al, 1998; Chin et al, 2003). A study in UK showed little agreement about treatment of SE in children; guidelines were absent or inadequate in 14 different centres, in only 5 specific timing for drug treatment was mentioned (Martland et al, 1998). Cascino et al (2001) mentioned also the inappropriate use of therapeutic regimens. In the retrospective evaluation of therapy in 184 cases, 72% received appropriate prompt medical treatment; in 76% the dose was less than recommended. The dose of the second treatment was inadequate in 80%.
It is considered essential by many to have a protocol with an adequate time schedule, in order to prevent unnecessary delay and to help to make a good choice between the various available drugs. This choice will be determined by speed of onset of action, duration of action and possible adverse effects. The anti-epileptic drugs used in the various phases may differ from one hospital to another, mainly based on previous experiences. Until recently comparative trials were lacking, contributing to the divergence in the used drugs. The current protocol has been based on the available literature on this subject, with special attention to available adequate comparative information and added with own experiences, especially when adequate comparative information was lacking (table 14a and 14b).

3.9.3.1 Pre-hospital treatment

GCSE most often starts outside the hospital; adequate information about the clinical presentation and duration is important. Physical examination may reveal signs of respiratory depression, motor asymmetries or external wounds. The treatment of choice with BDZ i.v. may enhance the risk of respiratory depression, whereas intravenous access will be difficult because of the convulsions. Rectal administration of DZP solution is the treatment of choice. Alternatives are midazolam (MDZ) i.m. and MDZ nasal or buccal. The use of BDZ i.v. by paramedics in the pre-hospital phase appeared safe

(Lowenstein et al, 1999; Alldredge et al, 2001) and in children caused a significant decrease of duration of SE and of admission (Alldredge et al, 1995). Intramuscular administration of fos-PHT may be considered to prevent treatment delay. When seizures persist 10 minutes after the rectal administration of DZP a second dose should be given and the patient should be transported to a local hospital with intensive care facilities. Recurrence of seizures after rectal administration of DZP after 20 - 30 min. is possible. Also in this case re-administration of the same amount of DZP and transport to the hospital is necessary. When the patient reaches the emergency room of a hospital all the measures taken in the pre-hospital phase and the transport to the hospital make it quite likely that at least one hour will have gone by since the onset of the GCSE.

3.9.3.2 Hospital treatment

On arrival at the hospital (emergency room) careful observation and physical examination is necessary. Prompt treatment of respiratory depression, hypotension and hyperthermia prevents unnecessary damage. Start oxygen supply and prevent aspiration by lateral semiprone position; apply an intravenous catheter; in some cases early intubation is necessary. Because of the probable high levels of catecholamine concentrations fluid administration in cases of hypotension is more appropriate than vasopressors (Benowitz et al, 1986). Treatment of acidosis will depend on systemic effects; even profound acidosis, however, has not been correlated with subsequent neuronal damage (Simon, 1985). In the mean time AED treatment should have been started; BDZ i.v. are first choice because of the speed of action and their few adverse events. LZP the choice of preference in the early phase of SE. The dose in adults is 2- 4 mg (< 2mg/min) and in children 0,05-0,10 mg/kg (< 2mg/min). In the Netherlands clonazepam (CZP) is used more often than LZP. DZP is not advised because of the high incidence of seizure recurrence; when used it must be combined with PHT loading. The dose of CZP is initially 1 mg in 30 sec; when seizures persist after the first 1 mg, repeated injections of 1 mg every 1 - 2 min. should be given. Failure, however, after 10 minutes of CZP use, means that PHT loading should be started.

Apart from AED treatment other measures may have to be taken: in alcoholics and completely unknown patients thiamine 50 mg i.v. and i.m.,

and glucose (50 ml 50%) administration is advised. Alcohol withdrawal is an increasing, although no major, cause or precipitating factor in GCSE (Pilke et al, 1984; Leppik et al, 1990). Apart from a thiamine deficiency, hypoglycaemia may be present too in alcoholics. Hypoglycaemia as a cause of GCSE or seizures has been reported (Malouf, 1985).

Thirty min. after admission to the emergency room, treatment according to this protocol will have stopped seizures in a large percentage of the patients. A part of them, especially elderly patients, have already been transported to the Intensive Care Unit (ICU), because of necessary monitoring (PHT loading) or mechanical ventilation. All those who still show seizures are transported to the ICU. Whenever possible, EEG monitoring should start as soon as possible, in order to monitor the effects of treatment and to establish a possible persistence of electrographic seizure activity.

3.9.3.3 Intensive Care Unit

Before considering barbiturates, a continuous infusion of MDZ might be considered. During MDZ infusion intubation and mechanical ventilation may be necessary. EEG-monitoring is necessary to investigate the presence of epileptic discharges because electrical status epilepticus will also have to be treated even if motor signs are subtle or absent. If half an hour after arrival at the ICU the GCSE persists (and in some cases earlier), all patients should be intubated, curarized and mechanically ventilated in order to prevent or treat medical complications. Normo-ventilation is advised; hyperventilation is not necessary in most cases, whereas severe hypocapnia (PCO_2 = 2Kpa) may prolong seizure duration (Bergsholm et al, 1984). Little is gained by using standard AED's as subsequent treatment when the first drug fails; rapid addition of general anaesthesia if the initial treatment fails appears logical (Treiman et al, 1997).

If seizures are still present (EEG-monitoring) after the use of MDZ infusion, general anaesthesia with propofol or thiopental treatment should be started. Others promote the use of PB before anaesthesia. Thiopental is administered via a central venous line. EEG monitoring is necessary, the dose of thiopental will be aimed at the amount which causes burst-suppression. When necessary because of hypotension, dopamine and/or dobutamine is started, via a second central venous line. Loading of thiopental is usually completed in 1 hour; the duration of continuous infusion depends

on therapeutically success. We suggest to taper thiopental slowly after 12 h; when seizures reappear, another period of burst-suppression is started, which will be maintained for 24 h and if necessary for 48-72 h. Failure after this is a grave sign; after 72 hours unsuccessful treatment switching to other drugs should be considered. Arterial blood pressure, and if possible intracranial pressure must be monitored. Haemodynamic monitoring (Swan Ganz) is useful.

Propofol is an alternative for barbiturate anaesthesia, with overall less serious adverse events and a much faster recovery. After a loading dose (2 mg/kg) a continuous infusion is started (5-10 mg/kg/hr), guided by the EEG. The dose should be reduced as soon as possible (to 1-3 mg/kg/hr) because of danger of metabolic acidosis, myocardial failure and rhabdomyolysis. We suggest tapering 12 hours after seizure activity is halted. The use of propofol requires the same ICU facilities as thiopental: the possibility of assisted ventilation, monitoring of arterial blood pressure, EEG monitoring, monitoring central venous pressure.

Although case reports have described success of drugs in patients refractory to barbiturate coma the overall results are variable and generally disappointing. Important in this respect is the fact that most patients refractory to the above mentioned protocol concern acute symptomatic cases with an inherent grave prognosis. The literature on drugs used in cases refractory to barbiturates or propofol is limited to case-reports, adequate comparative trials are completely lacking. Examples of therapy in this stage are treatment with CTZ, isoflurane and etomidate. Other reported possibilities are VPA, LZP infusion and MDZ infusion. Prior experience with a certain drug may be decisive then. Our own experience with CTZ is limited but not unfavourable, in contrast to our experiences with etomidate. The possibilities of calcium-entry-blockers (nimodipine, flunarizine) and NMDA-receptor-antagonists (MK-801, CGP-40116, NPC-17742, ketamine) should be further investigated, because they offer possible improvement of outcome, especially in these refractory cases (Bertram and Lothman, 1990; Walton, 1993; Walton and Treiman, 1994; Fujikawa et al, 1994; Borris et al, 2000; Yen et al, 2004).

Table 14a: Treatment of GCSE in adults according to protocol

Pre-hospital	– Make sure you are dealing with seizures. – Diazepam solution rectal: 10–30mg (0,5mg/kg). – Check for causes or complications that make hospitalisation mandatory. – Put patient in a lateral semi prone position. – When seizures persist 10 minutes after diazepam introduction arrange transportation to a hospital.
Hospital Emergency Room: 0-10 min.	– Observation, physical examination. – Establish an airway, oxygen by mask. – Lorazepam 2-4 mg i.v. or Clonazepam i.v. 1 mg. every 1-2 min. Until seizures stop or respiratory depression becomes evident.
Hospital Emergency Room: 10-30 min.	– Treatment of respiratory depression, hypotension, hyperthermia. – Insert in-dwelling intravenous and arterial catheter. – Blood for arterial blood-gas, anti-epileptic drug levels, glucose, electrolytes, renal and hepatic function test, CPK, full blood picture, drug-screen. – Glucose 50% i.v. 50 ml, Thiamine HCL 50 mg. i.v. and i.m. – If Lorazepam or Clonazepam fails after 10 min., start phenytoin-sodium 15-18 mg/kg, 50 mg/min. – If half an hour after admission seizures continue: transport to ICU.
Intensive Care Unit: 30-60 min.	– Endotracheal intubation; muscle relaxation (vecuronium), EEG monitoring. – Mechanical ventilation (normo-ventilation). – Midazolam infusion: bolus 0,1-0,3 mg/kg (5-10 mg, 4mg/min), followed by 0,05-0,40 mg/kg/hr.

Table 14b: Treatment of GCSE in adults according to protocol

Intensive Care Unit: after 60 min.	– Thiopental 10-30mg/kg (50-100mg i.v. every 2-5 min), maintenance dose 5-20 mg/kg/hr or Propofol bolus 2mg/kg, followed by infusion 5-10mg/kg/hr, reducing to 1-3mg/kg/hr (EEG guided). – EEG monitoring, Swan Ganz catheter. – If possible intracranial pressure monitoring. – If necessary dopamine, dobutamine (hypotension). – Adjust ventilation (PCO_2 may increase). – Moderate hypothermia (35°C).
Intensive Care Unit: after 12 hours.	– Taper thiopental or propofol after 12 hr – If seizure activity reappear increase thiopental or propofol until burst- suppression and maintain another 24 hr – (If necessary a final thiopental or propofol period of 48 hours).
Still no success: Consider one of the following drugs (in order of authors preference):	– Chlormethiazole. – Inhalation anesthesia (isoflurane). – Etomidate.
During treatment protocol:	– Establish the cause of GCSE (medical history, blood and CSF investigation, CT-scan/MRI, EEG). – Treatment of aspiration. – Prevent thrombosis, keratitis, gastric ulcer (stress). – Continue or start maintenance therapy of anti-epileptic drug.

Chapter 4

Generalized Convulsive Status Epilepticus: Causes, Therapy and Outcome in 346 patients

Epilepsia 1994; 35:1104-1112

Summary
We report data from 346 admissions for generalized convulsive Status Epilepticus (GCSE) in the Netherlands; 68% had had previously epilepsy. Outcome was determined by underlying cause, duration of more than four hours, the presence of more than one medical complication and the quality of therapy and management. Clonazepam, diazepam and phenytoin were most frequently used for treatment.

4.1 Introduction

Until 1962 no attempt has been made to achieve a classification or a proper definition of Status Epilepticus (SE). The conference in 1962 in Marseille on SE proposed a definition, which was approved by the ILAE in 1970: "A condition characterized by an epileptic seizure which is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition" (Gastaut, 1967). At the symposium in Santa Monica in 1980 a minimum duration of 30 min was added. SE thus currently encompasses a seizure of any type with a minimum duration of 30 min. and a succession of generalized convulsive seizures without regaining consciousness (Delgado-Escueta et al, 1983). Most patients with Generalized Convulsive Status Epilepticus (GCSE) can easily be treated with benzodiazepines (BDZ) and/or phenytoin (PHT). Cases refractory to common first- and second-line anti-epileptic drugs (AED) are mainly caused by acute symptomatic neurologic problems, such as brain tumours, encephalitis, cerebro-vascular accidents (CVA), head trauma and metabolic disturbances. In most such patients GCSE is the only (isolated) or presenting (initial) sign of epilepsy. GCSE can also occur in patients with previous epilepsy (intercurrent SE), precipitated by systemic infections, non-compliance, sleep deprivation and a miscellaneous group of more rare possibilities (Rowan and Scott, 1970; Heintel, 1972; Aminoff and Simon, 1980; Janz, 1983; Pilke et al, 1984; Goulon et al, 1985). Outcome in GCSE is especially determined by cause (Whitty and Taylor, 1949; Rowan and Scott, 1970; Oxbury and Whitty, 1971; Heintel, 1972; Celesia, 1983; Goulon et al, 1985). Acute symptomatic causes are more prevalent in older age groups, with corresponding worse outcome (Celesia et al, 1972; Sung and Chu, 1989). In cases admitted to the Intensive Care Unit (Goulon et al, 1985) a striking difference in mortality was noted

between the group of patients with an acute symptomatic cause (46%) and with previous epilepsy (8,6%). Outcome in cases with previous epilepsy is much better, whether aetiology was idiopathic, a chronic non-progressive encephalopathy or a remote symptomatic cause. The relation of SE duration to outcome is unclear. In an experimental animal setting pathophysiologic changes occurred after 30 min. Nevertheless some patients with SE duration of 90 or 120 min did not have problems (Rowan and Scott, 1970; Aminoff and Simon, 1980). Rowan and Scott (1970) reported increased morbidity in cases with duration of 10 hrs or more and mortality in cases of 13 hrs or more. Aminoff and Simon (1980) reported poorer outcome in cases with a duration of more than 120 min. De Lorenzo also noted a critical duration of GCSE with regard to outcome: mortality was only 5% in cases with duration of 1 hr or less, whereas mortality was 35% in cases of more than 60 minutes (De Lorenzo et al, 1987). A relation between duration of SE and outcome was not established by Clark and Prout (1903), Goulon et al (1985) and French et al (1988). Contributing to a longer SE duration are therapy delay (Whitty and Taylor, 1949; Rowan and Scott, 1970; Treiman et al, 1983; Lowenstein et al, 1988) and/or inadequate therapy (Delgado-Escueta and Enrile-Bascal, 1983; Celesia, 1983). Treatment according to a protocol might prevent this and improve outcome (Treiman et al, 1983). The sooner the AED treatment is initiated, the better the results (Walton and Treiman, 1988). Animal studies support the importance of adequate treatment of the medical complications during GCSE (Meldrum and Brierley, 1973; Meldrum et al, 1973; Meldrum et al, 1974; Siesjo and Wieloch, 1986). In human, the degree of metabolic acidosis did not correlate with outcome, whereas hyperthermia correlated with a poorer outcome (Aminoff and Simon, 1980). Despite optimal control of the various parameters such as pO2, pCO2, pH, blood pressure, and temperature in animal studies, neuronal damage occurred in substantia nigra pars reticularis after 30 min and in the third and fourth layer of the cerebral cortex or in special areas (CA1, CA4) of the hippocampus after 45-60 min (Nevander et al, 1984; Nevander et al, 1985; Meldrum, 1983; Siesjo and Wieloch, 1986). Calcium accumulation and excitatory aminoacids were important, although hypermetabolism, energy failure and lactate accumulation also played a role in producing the major neuronal damage in the substantia nigra.

We studied treatment practice and outcome of GCSE in The Netherlands paying particular attention to the contribution to outcome of duration, existence of medical complications and quality of therapy on outcome. Methods have been described in chapter 2.

4.2 Results

The Netherlands have a total population of nearly 15 million people, about 100.000 have epilepsy. SIG data for SE between 1980 and 1987 and our data for the same period are shown in fig. 1. The SIG data showed an average annual frequency of GCSE of 344, with a standard deviation (SD) of 82 (SIG, 1989). The reported annual mortality because of GCSE during the same period in cases of 15 yrs of age and older is 24, with SD 4 (CBS, 1989).

We identified 576 admissions for SE (all types), with 346 admissions for GCSE. Some general aspects of SE in relation to the hospital type are presented in table 1.

In smaller hospitals the number of acute symptomatic cases is lower than in university clinics or larger hospitals. The reverse is true for the occurrence of medical complications.

A striking feature is the number of incorrect diagnosis of SE, namely 118. These cases are documented as SE, reported as such to SIG, whereas file-investigation made clear that SE was not the case. In 75 cases it concerned a single seizure (63,5%), in 18 cases serial seizures (15,3%), in 12 cases the patient was known with previous epilepsy without any seizure problem at admission (10,2%) and in the remaining 13 cases various problems were present, but not related to epilepsy (11,0%). All further data concern the cohort of 458 patients who fulfilled our criteria for the diagnosis of SE.

If we restrict ourselves to GCSE (346 admissions), a slight male preference is noted and an increase in older age groups in the asymmetrical GCSE (table 2). The 346 admissions comprised 292 patients; 242 patients with one, thirty with two, six with three, four with four and one patient with ten admissions. Those who had more than 2 periods of GCSE were all patients with previous epilepsy, caused by head trauma, a chronic non-progressive encephalopathy, CVA or a progressive neurological disease. In 236 cases it concerned patients with previous epilepsy and 110 cases did not.

The causes of previous epilepsy in 236 cases of GCSE are presented in table 3. The 83 patients with a chronic non-progressive encephalopathy were mentally retarded and known with previous epilepsy. For most patients, the cause of the encephalopathy could not be established. The 8 patients with a progressive neurological disease of 1 case each of Alpers disease, Lafora body disease and a non-specified mitochondrial encephalomyopathy; in the remaining patients the cause was unknown. The miscellaneous group comprised multiple sclerosis (one), chronic psychiatric disease (one), autoimmune disease (two) and renal failure (one).

Fig. 1: Total number of SE reported to the SIG (SIG-data) and of this study, divided in the various types of SE*

Number of SE in the Netherlands		Total number of SE	
Total	3263	Total	576
GCSE	2751	GCSE	346
EPSE	337	EPSE	47
NCSE	175	NCSE	65
		NO-SE	118
SIG-data	(1980-1987)	This study	(1980-1987)

* GCSE = Generalized Convulsive Status Epilepticus; EPSE = Elementary Partial Status Epilepticus; NCSE = Non Convulsive Status Epilepticus; NO-SE = diagnosis of Status Epilepticus appeared wrong

Table 1: General aspects of SE in relation to hospital type (1980-1987)

	University Clinic (6)	Large Hospital (2)	Small Hospital (4)	Epilepsy Centre (2)
Average number of beds	890	717	460	–
Total number of SE (576)	300	113	98	65
Confirmed number of SE (458)	247	67	90	54
Previous epilepsy (%)	66,0	52,0	69,0	100
Mental Retardation (%)	17,5	7,0	28,0	39,0
Medical complications (%)	47,0	31,3	29,1	9,3
Acute symptomatic cause (%)	34,0	34,3	22,2	3,7
Morbidity (%)	18,5	10,4	7,7	1,9
Mortality (%)	11,7	11,9	6,7	1,9

Table 2: Distribution of age, gender and type in 346 admissions because of GCSE*

Type of SE	Male	Female	Age 15-30	Age 30-50	Age >50
GC-symmetrical	128	91	65	91	63
GC-a-symmetrical	67	53	32	24	64
Myoclonic	3	2	3	2	0
Tonic	0	2	1	1	0
Total	198	148	101	118	127

*Absolute numbers

Table 3: Causes of previous epilepsy in 236 cases of GCSE

Cause	N (%)
Chronic non-progressive encephalopathy	83 (35,2)
Head trauma	21 (8,9)
CVA	19 (8,0)
Post-operative (cerebral tumour, cyst, hygroma)	12 (5,1)
Progressive neurological disease	8 (3,4)
Encephalitis/meningitis	7 (3,0)
Alcohol	6 (2,5)
AVM/aneurysm	2 (0,9)
Miscellaneous	5 (2,1)
Idiopathic generalized epilepsy	6 (2,5)
Unknown	67 (28,4)
Total	236

Causes of GCSE and outcome

Previous epilepsy. Many patients (68%) had previous epilepsy (table 4). For a few patients an acute symptomatic cause was responsible for the GCSE (table 5a). The toxic causes (table 5a) consisted of amipaque (myelography), phenytoin-intoxication and carbamazepine-intoxication (one with a serum level 28 with good outcome and another with a serum level 32 mg/l, dead). Among the precipitating factors of GCSE problems with AEDs were the most prevalent (65), sometimes with fatal results (6,2% of these cases). Other

precipitating factors were alcohol, often combined with AEDs problems, and systemic infections. In 42,5% of the cases with previous epilepsy the cause or precipitating factor remained unknown.

Outcome in patients with previous epilepsy was favourable in 85,5%; morbidity was 8,5%, mortality 6% (table 4).

No previous epilepsy. The causes in patients without previous epilepsy but with a preceding neurological morbidity at least 3 months before the occurrence of SE were classified as remote symptomatic (table 5b). The acute symptomatic causes in patients without previous epilepsy are presented in table 5c. The types of brain tumour (table 5c) were varied and included: malignant lymphoma (two), metastases of sarcoma and of other malignant tumors (three), astrocytoma (grade 3 and 2-3), malignant meningeoma, corpus callosum glioma and tumors not further characterized (two). Metabolic problems (in table 5c) included hyperglycemia, renal failure with hypertension, hypokaliemia (2,2 mM in one case and 2,0 mM in another) and hyponatremia (121 mM). Toxic causes (table 5c) included 1 case each of cyclosporin, amipaque (myelography), cancer chemotherapy, maprotillin-intoxication, ethylene-glycol-intoxication, lidocaine and two cases of drug abuse. Morbidity and mortality in acute symptomatic cases was 23,3% each (table 4, 5c). Morbidity in remote symptomatic cases was 19%, mortality 14,3% (table 4, 5b).

Table 4: Causes of GCSE in relation to outcome in cases with and without previous epilepsy*

Outcome	Good (263)	Morbidity (45)	Mortality (38)
Previous Epilepsy (236)	202	20	14
Acute Symptomatic	7	3	4
Precipitating factors			
Non-compliance	56	5	4
Alcohol	14	0	0
Systemic infections	22	2	2
Unknown	100	7	3
Progressive neurological disease	3	3	1
No Previous Epilepsy (110)	61	25	24
Acute symptomatic	47	21	21
Remote symptomatic	14	4	3

* Absolute numbers

Table 5a: Acute symptomatic causes of GCSE in patients with previous epilepsy*

Outcome	Good (7)	Morbidity (3)	Mortality (4)
CVA	1	3	1
Encephalitis	0	0	1
Head trauma	1	0	1
Brain Tumour	1	0	0
Toxic	3	0	1
Cardiac arrest	1	0	0

* Absolute numbers

Table 5b: Remote symptomatic causes of GCSE in patient without previous epilepsy*

Outcome	Good (14)	Morbidity (4)	Mortality (3)
CVA	6	3	2
Encephalitis	1	0	0
Head trauma	2	1	0
Multiple sclerosis	1	0	0
Brain surgery	2	0	0
Chronic encephalopathy	2	0	1

* Absolute numbers

Table 5c: Acute symptomatic causes of GCSE in patients without previous epilepsy*

Outcome	Good (47)	Morbidity (21)	Mortality (21)
CVA	10	4	10
Encephalitis/meningitis	1	2	1
Metabolic	3	2	0
Head trauma	3	3	1
Brain tumour	5	4	2
Toxic	5	3	0
Alcohol	4	0	0
Cardiac arrest	0	0	4
Sleep-deprivation/ exhaustion	2	1	0
Hypoxia	0	1	0
Multiple sclerosis	1	1	0
Withdrawal benzodiazepines	1	0	0
Progressive neurological disease	1	0	0
Brain abscess	1	0	0
Systemic infection	5	0	0
Unknown	5	0	3

* Absolute numbers

Morbidity

The sequelae occurring after GCSE are presented in table 6. Decline of cognitive functions included persistent memory deficit, especially present in the group where SE-itself was responsible for morbidity. The miscellaneous group consisted of renal failure (because of SE), epilepsy, depressive mood, dysarthria, continuation of SE (further information was not present because of transport to another hospital) and hemi-anopsia (cause unknown).

Table 6: Morbidity after GCSE because of SE itself (SE) and underlying cause. In some cases the exact cause remained unknown (unknown)*

Morbidity	SE (12)	Cause (24)	Unknown (9)
Paresis	3	7	3
Cognitive Deterioration	4	8	3
Aphasia	2	0	0
Impairment of Consciousness	2	1	0
Ataxia	0	0	1
Miscellaneous	1	8	2

* Absolute numbers

Duration of GCSE and outcome

In 201 cases information about duration of GCSE was present. The causes of morbidity and mortality were divided in SE, cause and unknown. A relation between outcome and duration was evident in cases which GCSE itself was responsible for morbidity and mortality (table 7). When the underlying cause is responsible, duration seems not important; the damage is already present at the beginning. New neurological signs caused by the SE appeared in most cases after 4 hours, as did mortality in cases caused by GCSE (13 of the 15 cases). This was especially true after 8 hrs (12 cases).

Table 7: Relation between outcome and duration of GCSE; relative numbers*

Outcome	Good	Morbidity			Mortality		
		SE	Cause	Un-known	SE	Cause	Un-known
Duration							
< 2 hrs (73)	77,0	0	12,3	5,5	1,4	2,7	1,4
2 - 4 hrs (61)	80,3	1,6	6,6	1,6	1,6	8,2	0
4 - 6 hrs (13)	84,6	0	7,7	0	7,7	0	0
6 - 8 hrs (9)	66,7	11,1	0	0	0	22,2	0
8 - 12 hrs (5)	40,0	20,0	0	0	40,0	0	0
12 - 20 hrs (9)	55,6	11,1	11,1	0	22,2	0	0
> 20 hrs (31)	35,5	19,4	6,5	3,2	25,8	9,7	0
Total 100 (201)	69,5	5,0	8,5	3,0	7,5	6,0	0,5

* Absolute numbers between brackets

Medical complications and outcome

Medical complications in GCSE are to be expected in cases with duration of 2 hrs or more. We investigated the occurrence of medical complications in relation to outcome. In 41% one or more medical complications were present: hyperthermia (>38,5 °C), cardiac arrhythmias including cardiac arrest, respiratory insufficiency, aspiration, acidosis (<7,0; 7,0-7,1; 7,1-7,2; 7,2-7,3), hypotension, rhabdomyolysis, renal failure, hepatic failure and intracranial hypertension. Renal or hepatic failure and rhabdomyolysis were observed in cases with several medical complications. The increase of CPK was over 10000 U/L in three patients, with myoglobin in the urine; one patient had values of more than 150000 U/L. One patient had rhabdomyolysis with a CPK increase of only 1809 U/L with the presence of myoglobin in the urine.

The existence of more than one medical complication was related to poor outcome (table 8). Most important were respiratory insufficiency and aspiration, although cardiac arrhythmias and hypotension also contributed to a poor result. In severe cases renal or hepatic failure and/or intracranial hypertension were very grave signs (table 9). Although acidosis and hyperthermia may contribute to less favourable results, a relation between the degree of acidosis or hyperthermia could not be established.

Table 8: Number of medical complications in relation to outcome; relative numbers*

Outcome	Good	Morbidity			Mortality		
Complications		SE	Cause	Un-known	SE	Cause	Un-known
No (204)	85,3	2,0	6,4	2,0	1,0	2,0	1,5
1 (82)	73,2	4,9	9,8	2,4	2,4	6,1	1,2
>1 (60)	48,3	6,7	5,0	5,0	28,3	5,0	1,7

* Absolute numbers between brackets

Table 9: Medical complications in GCSE in relation to outcome, relative numbers*

Outcome	Good	Morbidity			Mortality		
Complications		SE	Cause	Un-known	SE	Cause	Un-known
No (204)	85,3	2,0	6,4	2,0	1,0	2,0	1,5
Respiratory insufficiency (58)	48,3	6,9	5,2	5,2	24,1	8,6	1,7
Hyperthermia (48)	56,3	14,6	8,3	2,1	12,5	6,3	0
Acidosis (43)	60,5	4,7	7,0	7,0	14,0	7,0	0
Aspiration (21)	42,9	9,5	9,5	0	33,0	4,8	0
Renal and/or hepatic failure (20)	15,0	15,0	5,0	10,0	42,9	5,0	5,0
Hypotension (17)	53,0	0	11,8	5,9	23,5	0	5,9
Cardiac Arrythmias (13)	61,5	7,7	0	0	23,1	7,7	0
Intracranial hypertension (4)	25,0	0	0	0	75,0	0	0
Rhabdomyolysis (4)	25,0	25,0	0	0	50,0	0	0

* Absolute numbers between brackets

Therapy and management of GCSE

We tried to determine the effect of quality of the therapy of GCSE on outcome. In 263 admissions with good outcome, therapy was good or sufficient in 85,6%, and was insufficient in 10,3% (table 10), mainly because of inadequate dosage of AEDs (8%). In patients with sequelae (45 admissions) inadequate therapy was evident in 22,2%.

In cases where morbidity was due to SE itself insufficient therapy was even more frequent (50%). Of the total number of patients who died (38) therapy was insufficient in 44,7%. In cases due to SE itself these results were again worse, occurring in 62% with insufficient dosage of AEDs the major problem (table 10).

We determined last administered AED either before successful cessation of SE or before death: BDZ and/or PHT were administered most frequently (table 11). Thiopental, clorazepate and etomidate were administered when

BDZ and PHT were without effect; chlormethiazole was administered after failure of thiopental.

Table 10: Therapy in relation to outcome; absolute numbers

Outcome	Good (263)	Morbidity (45)			Mortality (38)		
Therapy		SE	Cause	Un-known	SE	Cause	Un-known
Good	225	6	21	8	8	11	2
No therapy	11	0	0	0	0	0	0
Inadequate (total)	27	6	3	1	13	3	1
Dose	21	0	2	0	9	1	1
Route	5	0	0	0	0	0	0
Delay	1	3	1	0	0	0	0
No ventilation	0	2	0	0	2	2	0
No EEG	0	1	0	1	2	0	0

Table 11: Last given therapy in GCSE*

Therapy		Number
No therapy		15
Diazepam	i.v.	58
	rectiole	9
	i.m.	2
	+ PHT	29
Clonazepam	i.v.	82
	i.m.	2
	+ PHT	26
PHT	i.v. shot	44
	i.v. loading	36
	i.m.	2
Midazolam	i.v.	4
Clorazapate	infusion	6
Etomidate	infusion	5
Thiopentone	i.v. shot	3
	infusion	16
Chlormethiazole	infusion	2
Chloralhydrate	rectal	2
Lidocaine	i.v.	1
Other		2
Total admissions		346

* Absolute numbers

4.3 Discussion

Between 1980-1987 every year about 344 ± 82 admissions occur for GCSE in the Netherlands (population 15 million) in patients of 15 yrs of age and older (SIG, 1989). We studied 346 admissions for GCSE, gathered from 12 hospitals and two epilepsy centres, spread all over the country. We showed that the numbers of patients with GCSE as reported by the SIG are relatively high, because in a considerable number the diagnosis appeared wrong (118 cases from a total of 576). In larger hospitals and University Clinics the relative numbers of acute symptomatic causes is higher in comparison to

smaller hospitals and epilepsy centres, with comparable worse outcome. Transfer of therapy resistant and more complicated cases to University and larger hospitals with more facilities may contribute to this result.

The distribution of GCSE in male or female patients shows some preference for the male (57,2%). Some of the reports in the literature confirm this male predominance (Heintel, 1972; Aminoff and Simon, 1980; Celesia, 1983); other reports show no difference (Clark and Prout, 1903; Rowan and Scott, 1970; Pilke et al, 1984; Goulon et al, 1985). In patients of 50 years and older a high percentage of acute symptomatic causes is present (65%), in agreement with previous reports (Celesia, 1972; Heintel, 1972; Sung and Chu, 1989).

Of the 346 admissions for GCSE, 236 were known with previous epilepsy. Patients with more than one episode of GCSE all had previous epilepsy. The causes of previous epilepsy, shown in table 3, were mainly chronic non-progressive encephalopathy or unknown.

Outcome in cases of GCSE caused by an acute neurological cause, whether in patients known with previous epilepsy or without previous epilepsy, appears comparable (table 4).

Important with regard to outcome in patients with previous epilepsy are non-compliance (and other AED problems) and systemic infections. Precipitating factors were similar to those previously reported (Rowan and Scott, 1970; Heintel, 1972; Aminoff and Simon, 1980; Pilke et al, 1984; Goulon et al, 1985). That AED non-compliance may be fatal should be stressed. The difference in outcome between patients with and without previous epilepsy is striking (table 4 and 5) and agrees with previous reports, but we observed a lower frequency of brain tumours (Oxbury and Whitty, 1971; Roger et al, 1974; Janz, 1983; Pilke et al, 1984), which was more comparable to frequencies observed more recently (Aminoff and Simon, 1980; Celesia, 1983; Goulon et al, 1985). The frequency of CVA was similar to that in previous reports (Aminoff and Simon, 1980; Pilke et al, 1984; Goulon et al, 1985). Other causes did not significantly differ from those in previous reports.

To investigate the contribution of GCSE itself to outcome, we made a distinction between cases in which outcome was determined by the underlying cause and cases in which GCSE was the main determinant. When we considered duration of GCSE with regard to outcome, the importance of

such a distinction becomes clear. Although other authors showed a relation between duration and outcome (Rowan and Scott, 1970; Heintel 1972), only Aminoff and Simon (1980) made a distinction between underlying cause and SE itself.

We established a relation between outcome and duration, especially in cases where GCSE itself was responsible. Duration of four hours or more caused an increase in morbidity and mortality, comparable to the data of Aminoff and Simon (1980) and in agreement with experimental results (Meldrum, 1983; Lothman, 1990). Some authors failed to establish a relation between outcome and duration, which may be explained by the lack of differentiation between underlying cause and the effect of SE itself (Goulon et al, 1985; French et al, 1988).

The importance of prompt treatment of medical complications during GCSE has been stressed (Glaser, 1983; Meldrum, 1983; Simon, 1985; Lothman, 1990). We have shown a major negative contribution to outcome when more than one medical complication was present. In particular, respiratory insufficiency (and aspiration), cardiac arrhythmias and hypotension are related to a negative outcome. Patients with renal and/or hepatic failure or with rhabdomyolysis had an especially bad outcome; these conditions usually occur in combination with other medical complications. We did not establish a relation between the degree of acidosis (Aminoff and Simon, 1980) or between the degree of hyperthermia and outcome. Intracranial hypertension was measured in only a few cases; three of these four patients died.

Important to the existence of several medical complications was inadequate management: “A major mistake is to wait for a drug to work” (Simon, 1985). Of patients who died 44,7% had had inadequate AED therapy, 22,2% of those with sequelae and in only 10,3% with good outcome.

The general mode of treatment was rather similar in all hospitals: BDZ and/or PHT, followed (when necessary) by thiopentone, and in fewer cases, by clorazepate or etomidate. Chlormethiazole was only used when thiopentone was without success.

Our results show that outcome in GCSE is particularly determined by the underlying cause, but also influenced by a duration of more than four hours, by the existence of 1 or more medical complications and by insufficient

therapy. A treatment protocol, including a time schedule, can be used to prevent unnecessary delay, promotes a logical sequence of administration of the various AEDs and contributes to a better outcome (Treiman et al, 1983; Scholtes et al, 1993). An example of such a protocol is presented in table 14a-14b (chapter 3.9).

Chapter 5

Non-Convulsive Status Epilepticus: Causes, Therapy and Outcome in 65 patients

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Summary
The incidence of Non-Convulsive Status Epilepticus (NCSE) in The Netherlands is not known. We studied 40 cases with Complex Partial Status Epilepticus (CPSE) and 25 with Absence Status Epilepticus (ASE), from 12 hospitals and 2 epilepsy centres, spread all over the country during the period 1980-1987. We restricted ourselves to adult patients (older than 15 years). The clinical presentation made distinction between CPSE and ASE possible in a number of cases. Focal clinical signs were more frequent in CPSE; a fluctuating level of consciousness was more often present in ASE. All cases, but one, with ASE and most cases with CPSE (28) were known with previous epilepsy. Outcome in ASE was good in all. Outcome in CPSE was determined by underlying cause and quality of therapy. In one patient morbidity appeared to be caused by the discharges themselves.

5.1 Introduction

Non-convulsive Status Epilepticus (NCSE) is characterized by a clouding of consciousness, confusion, automatisms and amnesia, with specific EEG abnormalities in accord with the type of NCSE. In adult patients NCSE is divided in two main groups, generalized NCSE and complex partial status epilepticus (CPSE), which because of their clinical similarities have been discussed together by most authors. Generalized NCSE includes absence status epilepticus (ASE) and atypical absence SE. ASE was described first by Lennox in 1945, since then several reports have appeared which describe ASE under a variety of names: absence SE, petit mal SE, epilepsia minor continua, spike-wave stupor and prolonged petit mal automatisms. At the moment ASE is the most frequent used term to describe a prolonged confusional state of varying severity, with a fluctuating level of consciousness together with generalized paroxysmal activity on the EEG (Andermann and Robb, 1972; Porter and Penry, 1983; Guberman et al, 1986). In this paper ASE is equivalent to generalized NCSE. The first description of CPSE was in 1956 by Gastaut (Gastaut et al, 1956). Others have described the clinical presentation extensively (Richard and Brenner, 1980; Treiman and Delgado-Escueta, 1983; Williamson et al, 1985; Tomson et al, 1986; Delgado-Escueta and Treiman, 1987; Tomson et al, 1992).

This study concerns patients admitted to hospitals. Methods have been described in chapter 2. We tried to find out how the diagnosis of a particular type of NCSE had been made and we were especially interested in clinical presentation, management and outcome. Some cases with NCSE will not be diagnosed, or will not be sent to a hospital if the NCSE subsided spontaneously. Others are known to have had previous epilepsy or previous episodes of NCSE and immediate hospitalisation is not always required.

5.2 Results

We found in 12 hospitals and 2 epilepsy centres a total number of 65 admissions for NCSE, 40 with CPSE and 25 with ASE. The distribution of age and gender is presented in table 1. The patients with CPSE are mainly from university clinics (22) and epilepsy centres (16), cases with ASE from small and large general hospitals (10) and epilepsy centres (10).

Table 1: Distribution of age and gender in patients with CPSE and ASE*

Age	Age 15 - 30		Age 30 -50		Age > 50	
	Male	Female	Male	Female	Male	Female
CPSE						
Previous epilepsy (28)	9	3	5	3	5	3
No previous epilepsy (12)	0	1	1	2	3	5
ASE						
Previous epilepsy (24)	5	4	0	1	4	10
No previous epilepsy (1)	1	0	0	0	0	0

* Absolute numbers

Absence Status Epilepticus (ASE)

The number of admissions because of ASE was 25 in 18 patients. One female patient of 72 years had six admissions and two patients had two admissions each. Only one patient had no history of previous epilepsy (table 1). Two patients with ASE were mentally retarded; the EEG showed continuous spike-slow-wave activity (atypical ASE).

The clinical presentation of ASE was characterized by a state of altered consciousness. Some appeared alert, but responsiveness was impaired. Others behaved strangely; they were laughing without obvious reason and showed myoclonic jerking of eyelids. Some showed automatisms, either environmentally induced or spontaneous. A few patients were very drowsy and did not speak; others were withdrawn and showed stereotypic automatisms such as smiling and head nodding. A state of confusion with fluctuating level of consciousness was present in 8. Two patients were incontinent for urine; both were very drowsy. One patient wandered around and showed myoclonic jerks especially in the arms.

EEG investigation confirmed the diagnosis of ASE in 21 cases. Continuous bilateral spike-wave activity of 2-3 Hz was present in 10 patients; continuous bilateral poly-spike-wave activity was found in 7 cases. In two patients a discontinuous EEG-pattern was present with bilateral spike-wave-activity of 2½-4 Hz. In two patients with atypical absence SE slow-spike-wave-activity had been found. In two patients no EEG had been performed; both were known with previous idiopathic generalized epilepsy with absence seizures.

EEG investigation had confirmed the diagnosis of ASE in four admissions of a female patient of 72 years; during two further admissions EEG investigations had been considered unnecessary.

Precipitating factors of ASE in the 24 cases with previous epilepsy consisted of antiepileptic drug withdrawal or non-compliance (10), systemic infection (1) and stress (1); in 11 cases no cause could be found. One patient exhibited several periods during one admission of ASE each time recurring after defecation. The cause of ASE in one patient without previous epilepsy remained unknown.

Outcome in ASE was good in all patients, irrespective duration of SE. Duration was less than two hours in eight, including one case of atypical ASE; between two and twenty hours in ten, 24 hours in four, 48 hrs in two

(including the other case of atypical ASE) and 14 days in one patient. Last given therapy of ASE is presented in table 2.
The quality of therapy appeared insufficient in three patients; outcome was good all the same.

Complex Partial Status Epilepticus (CPSE)

CPSE concerned 40 admissions in 37 patients; 3 male patients had 2 admissions each and were all three known with previous epilepsy. A male or female preference in CPSE was not present. Most patients without previous epilepsy were older than 50 years of age (table 1). Those with a history of previous epilepsy were all known with complex partial seizures, with or without secondary generalized seizures.

CPSE followed one or more tonic-clonic seizures in ten patients, a tonic-clonic seizure occurred during CPSE in one patient and ended CPSE in two patients.

The clinical presentation of CPSE was characterized by confusion and slowness in response, together with stereotypic and/or complex automatisms. Focal clinical signs, such as clonic jerking of 1 arm, were present in almost half of the cases, whereas tonic deviation of eyes and head was present in another 15%.

About 50% of the patients showed a succession of complex partial seizures; between the seizures the patients remained confused or unresponsive. Others remained in a continuous state of confusion and were both withdrawn without initiative and hardly responsive, or appeared restless with various automatisms, such as lip smacking and picking at clothes or objects. Two appeared to have hallucinations. Staring (motionless) was seen in only 2 patients.

EEG investigation had been done in 18 patients. Focal epileptic activity was present in 10 patients, confirming the diagnosis of CPSE. Patients with bilateral slow wave activity (2) or bilateral spike-slow wave or poly spike-wave activity (4) were all known with previous partial epilepsy. In 15 cases with previous partial epilepsy EEG investigation had not been done and the diagnosis of CPSE had been based on clinical presentation in a patient known with partial epilepsy. In 7 patients without previous epilepsy the diagnosis of CPSE had been made without EEG investigation based on clinical presentation together with an acute or remote symptomatic cause

with obvious focal characteristics and on the results of anti-epileptic drug treatment.

In patients with previous epilepsy problems with therapy such as non-compliance were the most frequent precipitating factor (12 cases). On two occasions systemic infection, on one occasion stroke, and another one stress triggered the CPSE. In 12 cases the cause remained unknown.
In patients without previous epilepsy various acute symptomatic causes were present: stroke (two), brain tumour (two), pneumococcal meningo-encephalitis (one), carcinomatous meningitis and lung cancer (one), digoxine intoxication (one), pneumococcal pneumonia (one), and a case without a clear cause.

Three patients had remote symptomatic causes: multiple sclerosis, global cerebral atrophy and chronic dialysis and aluminium encephalopathy.

Outcome in cases with previous epilepsy was good in all but one, a 78 years old man who had successful treatment stopping his CPSE but died four days later because of aspiration pneumonia, acquired during the SE.

In patients without previous epilepsy six had sequelae after CPSE: paresis because of underlying cause (two), persistent cognitive disturbances because of underlying cause (one) and of unknown cause (one) and persistent impaired consciousness of unknown cause (one).

The CPSE itself caused morbidity in a female patient (74 years) who developed CPSE lasting 24 hours after digoxine intoxication; she was confused with jerking of the right arm, alternating with short periods of staring. After treatment with AED and recovery from CPSE this patient exhibited word finding problems and a memory deficit. Patients with morbidity were, except for one (38 years), older than 60 years. In patients without previous epilepsy one patient of 67 died because of the underlying cause (lung cancer and carcinomatous meningitis).

Duration of CPSE was less than two hours in 17, between two and four hours in nine, between four and twelve in five, one to three days in seven patients, four 4 days in one and 16 days in another patient. When the underlying cause was responsible for morbidity (three patients), the damage is present at the start of CPSE; in two of these three cases duration of CPSE was less than 2 hrs. The patient with morbidity because of CPSE itself remained in status for 24 hrs. Notwithstanding duration of CPSE from 20 hours to 16 days all patients except one had a good outcome.

Last given therapy that ended CPSE is presented in table 2. The quality of therapy was studied in order to examine the relation between outcome and therapy. In 32 cases with good outcome therapy was inadequate in 4 patients (12½%). In 6 cases with sequelae therapy was insufficient in three. In one of these patients this may have contributed to persistent morbidity because of CPSE itself, because when phenytoin i.v. had no success, an attempt to initiate carbamazepine therapy was started, but loading was not employed. Though eventually the patient got out of CPSE, the delay was probably too long. Another patient with insufficient therapy concerned a 38 years old man with CPSE caused by pneumococcal meningitis with duration of 4 days. Every two minutes he showed a seizure (EEG confirmed). He was treated with phenytoin i.v. (no loading), clonazepam 6 mg/hr during two days and 6 x 100 mg i.v. phenobarbital. He suffered a persistent paresis of the left arm that was in accordance to the EEG focus. In this case it was difficult to judge whether the infection or the CPSE contributed most to the paresis.

The third case with insufficient therapy concerned a male patient of 79 years who presented with CPSE of 35 minutes duration followed by persistent depressed level of consciousness. The EEG showed various periods of generalized SE. Treatment consisted of phenytoin loading, 1 mg clonazepam and 8 mg diazepam i.v., without any effect on the electric SE. This patient was known with prostate carcinoma with metastases. A cerebral metastasis could not be found. Outcome was waited for without active intervention and the patient was transferred to a nursing home.

Table 2: Last given therapy in CPSE and ASE*

Treatment of NCSE		CPSE	ASE
No treatment		4	2
Diazepam	i.v.	6	6
	rectal	3	2
Clonazepam	i.v.	13	8
	i.m.	0	1
	rectal	1	2
Phenytoin	i.v.shot	6	2
	loading	2	0
Thiopental		1	0
Chloralhydrate		2	0
Other drugs		2	2

* Absolute numbers

5.3 *Discussion*

The literature on NCSE is extensive but sometimes confusing. Even some patients with previous partial epilepsy have been described as having ASE instead of CPSE (Niedermeyer et al, 1979; Guberman et al, 1986; Tomson et al; 1986). Others draw general conclusions about patients with NCSE, whereas different types of NCSE are present (Guberman et al, 1986; Fagan and Lee, 1990). The distinction on clinical grounds alone between the various types of NCSE is difficult, but some clinical features favour the diagnosis of CPSE (focal clinical signs, tonic deviation of eyes and head), whereas others are more present in ASE (fluctuating level of consciousness, rhythmic blinking). The EEG in NCSE is necessary to differentiate between the various types of NCSE but also to distinguish NCSE from e.g. a psychiatric diagnosis. Generalized epileptic discharges or the absence of epileptic activity do not exclude CPSE, however.

Most admissions in our study were for CPSE, which confirms the conclusion of Tomson et al (1992) that CPSE is more frequent than previously reported. This may be caused by the fact that the ICD-9 did not include CPSE.

Age distribution in cases of CPSE showed no preference in patients with previous epilepsy, but in cases without previous epilepsy most patients were older than 50 years of age.

Clinical presentation and causes of CPSE were in accordance with the literature. A relation between outcome and duration could not be established. Morbidity after CPSE is often caused by the aetiology, such as a stroke or brain tumour, less often by the continuing discharges themselves (Engel et al, 1978; Treiman and Delgado-Escueta, 1988). Morbidity because of CPSE was suggested in one case. In our group of CPSE inadequate therapy may very well have contributed to a worse outcome in 3 cases.

In ASE all but one patient had idiopathic generalized epilepsy. In ASE we did not find a female preference, although women outnumbered men in the elderly age group. In our patient group with ASE no cases were present with situation related ASE or ASE de novo in the elderly. Precipitating factors in ASE were in accordance to the literature, the same goes for therapy and outcome. Duration was less than 24 hrs in 70% of the cases.

Although outcome in ASE was good in all cases, several showed inadequate therapy.

While examining the patient records in the participating hospitals we were struck by the variety of treatments employed to stop SE. Some procedures were clearly inadequate.

We recommend the same protocol as that used in generalized convulsive SE (Scholtes et al, 1993).

Chapter 6

Simple Partial Status Epilepticus: causes, therapy and outcome in 47 patients

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Summary
We conducted a retrospective case-note review of 47 patients of 15 years and older who had sustained simple partial status epilepticus (SPSE) in the Netherlands between 1980 and 1987. In 46 patients the type of SPSE was somatomotor (in four adversive) and in one aphasic with visual and auditory hallucinations. SPSE was more common over the age of 50. Six of 27 patients with previous epilepsy had an acute symptomatic cause. In 20 patients without previous epilepsy stroke was the most frequent cause (75%). Outcome was especially determined by the underlying cause. In one patient the continuing epileptic activity may have caused neuronal damage.

6.1 Introduction

Simple Partial Status Epilepticus (SPSE) is characterized by partial seizures without impairment of consciousness or secondary generalization, and with preserved neurovegetative regulation (Gastaut, 1983). The clinical expression depends on the region of the brain where the seizures originate. The most frequent type of SPSE is somatomotor. Other types include aphasic and somatosensory. Partial seizures with preserved consciousness are called SPSE when continuous clinical and electro-encephalographic seizures are present for at least 30 minutes (Delgado-Escueta and Treiman, 1987).

In general neurological practice two groups of patients with SPSE prevail:
1. Those with a succession of simple partial seizures with Jacksonian march, without persistent segmental myoclonus (somatomotor SPSE).
2. Those with persistent myoclonus in a limited area of the body, present for weeks or months and sometimes in combination with somatomotor or tonic-clonic seizures (Epilepsia Partialis Continua).

Both types are usually caused by a symptomatic brain lesion, but may also occur in patients known with a history of previous epilepsy.

Somatomotor SPSE is synonymous with Epilepsia Partialis Continua (EPC) when myoclonic jerks are continuously present in the same body parts affected by the somatomotor seizures (Delgado-Escueta and Treiman, 1987; Thomas et al, 1977; Schomer, 1993). Most case studies or reviews concern EPC; other types of SPSE have only rarely been described (Schomer, 1993;

Lohler and Peters, 1974; Juul-Jensen and Denny-Brown, 1966; Meienberg and Karbowski, 1977; Andermann et al, 1986). As part of a study on SE in The Netherlands we were able to study retrospectively 47 adult patients of SPSE. Methods have been described in chapter 2. We were particular interested in the various types of SPSE, the causes, EEG findings, therapy and outcome.

6.2 Results

The admissions we retrieved covering a period of eight years concerned 47 patients, 27 were known with a history of epilepsy. The causes of previous epilepsy were symptomatic in 18, whereas in nine patients the cause remained unknown. In five patients SPSE ended with a generalized tonic-clonic seizure, in seven a tonic-clonic seizure preceded SPSE. In our material a female preponderance of 30 versus 17 males was found (table 1).

Table 1: Distribution of age and gender*

Male	Female	Age 15-30	Age 30-50	Age >50
17	30	2	14	31

* Absolute numbers

Types of SPSE

Apart from one patient with aphasic SE all showed somatomotor SPSE; four of these had adversive SPSE. The facial musculature was involved in 38 patients, alone (eight) or in combination with the eyes (one), an arm (seven), platysma (two), and an arm and a leg (20). In four patients jerking was limited to an arm (one), a hand (two) or the abdominal wall (one).

The patient with aphasic SPSE was a woman aged 67, known with previous epilepsy (caused by stroke), who developed SPSE with duration of 5 days. The clinical presentation consisted of aphasia, acoustic hallucinations (strange sounds, music, voices), left sided headache and visual hallucinations (red balls before right eye). She remained alert and showed on the EEG recurrent epileptic seizures starting left occipital with a 13 Hz sharp wave activity, changing to spike-wave activity (3-4 Hz) and spreading over the

left hemisphere. Sometimes a start was seen in the left paracentral region. Further investigations could not establish a cause. When the EEG showed that the SPSE had been arrested the patient continued to exhibit persistent word-findings problems and a slight verbal memory deficit.

In 26 of 46 patients with somatomotor SPSE, frank seizures were evident without documented continuous myoclonus. The remainder, 20, showed more or less continuous clonic or myoclonic jerks, corresponding to EPC. When we compared the patients of EPC to those without continuous myoclonus, no differences were found between these two groups of patients with regard to outcome, number of patients with previous epilepsy or causes.

During SPSE EEG investigation was made in only thirteen patients that showed abnormal findings corresponding to the clinical expression in twelve of them. However, specific epileptic discharges were present in only 5 patients. Brain CT-scan was performed in all; MRI, PET or SPECT in none.

Causes of SPSE

In 27 patients with previous epilepsy six developed SPSE because of a new neurological problem: metastases (two), stroke (one), pneumococcal meningitis (one), osteomyelitis of the skull (one) and hypocalcaemia (one). Compliance problems (anti-epileptic drugs) were only present in three patients. In three patients a systemic infection was considered to be the precipitating factor. In 15 patients the cause remained unknown.

In 20 patients without previous epilepsy stroke appeared the most prominent cause (14). In three patients a brain tumour had been found, while in another three patients a cause could not be established.

Duration of SPSE

Duration was less than two hours in 13 patients, between two and four hours in 12, between four and 20 hours in four and longer than 20 hours in 18 patients. Half of these had duration of one to three days, the other half between three and 14 days. Exceptional long duration (7 weeks or more than 1 year) was seen in three patients with continuous focal myoclonic jerks (EPC).

Outcome of SPSE

Four patients died, all due to cerebral infarction. Morbidity after SPSE was present in 10 patients and consisted of paresis (four), aphasia (two), psychiatric disturbance (one), cognitive impairment (two) and persistent impairment of consciousness (one). Morbidity was mainly due to the underlying cause (six patients); in three patients the exact cause of morbidity could not be established. Morbidity in one patient was attributed to SE itself. In the patients with sequelae because of the underlying cause (six), four had had a cerebral infarction, one a subdural haematoma and one an intracerebral haematoma. The patients with sequelae of unknown cause were all known with previous epilepsy.

Table 2: Causes of EPSE in relation to outcome*

Causes of EPSE	Outcome good	Morbidity	Mortality
Previous Epilepsy (27)			
Acute Neurological Cause	6	0	0
Anti-epileptic Drugs	3	0	0
Systemic Infection	2	1	0
Unknown	12	3	0
Total	23	4	0
No Previous Epilepsy (20)			
Stroke	4	6	4
Brain tumour	3	0	0
Unknown	3	0	0
Total	10	6	4

* Absolute numbers

Treatment

Last therapy administered just before SPSE ended or given as a last try consisted mainly of benzodiazepines, in particular (40%) clonazepam or clonazepam with phenytoin. Other drugs were intravenous phenytoin, diazepam, lidocaine, etomidate infusion, thiopental infusion, carbamazepine and intravenous calcium in a case of hypocalcaemia. In this last case calcium was immediately successful, whereas diazepam and clonazepam failed.

When outcome is related to quality of therapy we found in patients with good outcome that therapy was inadequate in 21%; in patients with morbidity in 40%, and in patients with fatal outcome in 50%.

6.3 Discussion

SPSE is relatively rare and most case reports and reviews concern EPC, also named somatomotor SPSE (Schomer, 1993). We did not find specific differences between patients with continuous clonic or myoclonic activity and patients with partial motor seizures with regard to cause, outcome and the presence of previous epilepsy. Our findings differ from those published for the frequency of previous epilepsy in patients with SPSE. Duration of SPSE in our series was generally shorter than mentioned in the literature and we differ with respect having a higher prevalence of female patients.

The cause of SPSE in our 20 patients without previous epilepsy was stroke in 70%, a brain tumour in 15% and unknown in another 15%. Two of the latter patients had a chronic psychiatric disease and one a remote symptomatic cause (subarachnoidal haemorrhage some years earlier). But also in patients with previous epilepsy an acute neurological problem appeared a prominent cause (22%).

No correlation could be established between outcome and duration. Outcome was mainly determined by the underlying cause. In three patients the cause of morbidity remained unknown. All three were known with previous epilepsy; one was suspected to have a brain lesion, but the exact nature was not known; another was known with mental retardation and the third had epilepsy because of stroke and a new cerebrovascular accident was suggested but this could not be determined with certainty. Only in one case SPSE itself as a cause of morbidity was likely.

Continuing seizure activity as a cause of morbidity in partial SE has been established in complex partial SE (Engel et al, 1978). SPSE as a cause of morbidity only has been suggested in some other patients (Knopman et al, 1977; Duncan et al, 1990).

In SPSE, like in GCSE (Scholtes et al, 1994) we found that therapy was more often inadequate in patients with less good outcome, but the number of patients with mortality or morbidity was too low to draw conclusions.

Treatment of SE irrespective of type should occur according to protocol (Scholtes et al, 1993). During treatment adequate medical care with special attention for the respiration is essential. The cause of SPSE should be established as soon as possible, maintenance therapy with anti-epileptic drugs should be continued or started. In therapy-resistant patients surgical treatment may be considered (Bancaud et al, 1982).

Chapter 7

Status Epilepticus in Children

Seizure 1996; 5: 177-184.

Summary

Aetiology and outcome of status epilepticus (SE) in children are different in comparison with adult patients. The main characteristics of SE in 112 children (age 6 months- 15 years) are presented, with special attention to age, duration of SE, causes, medical complications and therapy. The greater part of these children was known with previous epilepsy, a considerable number with mental retardation. Outcome in convulsive SE is influenced by cause, duration, age, the occurrence of medical complications and quality of treatment. Outcome in non-convulsive SE is good and does not seem to be influenced by the treatment strategy. The use of a therapy protocol may prevent unnecessary delay and contribute to a better outcome.

7.1 Introduction

Status epilepticus (SE) is a major neurological and medical emergency requiring treatment to prevent significant brain damage and possible mortality. SE is a seizure with a minimum duration of 30 min; any seizure type may extend to SE. A succession of generalized convulsive seizures without regaining consciousness is considered SE too (Delgado-Escueta et al, 1983). The limit of 30 min. is not a random choice; beyond that period various pathophysiologic changes occur, starting in the substantia nigra (Nevander et al, 1984; Nevander et al, 1985). These pathophysiologic changes occur mainly in generalized convulsive SE (GCSE) and are important with regard to outcome. Because of various unique features of SE in the neonatal brain we discuss SE only in children beyond the neonatal period. In the general population both the very young and the elderly represent the populations most at risk for developing SE. The number of cases has a slight peak at <1 year of age and gradually decline until early adulthood (DeLorenzo et al, 1992). Mortality in children is lower (2-3%) than in adult patients (25%); mortality increases with age and depends on the underlying cause (DeLorenzo et al, 1992). The causes of SE are divided in idiopathic, remote symptomatic, febrile, acute symptomatic and progressive encephalopathy. Children without previous epilepsy are relatively younger, with longer seizure duration and a longer postictal coma. SE is the initial presentation of epilepsy in 8-12% and occurs in 10-20% during the course of epilepsy,

especially in cases of symptomatic epilepsy. Recurrent SE occurs mainly in children with an underlying neurological abnormality (Shinnar et al, 1992). The risk of epilepsy following SE is increased in acute and remote symptomatic cases, but not in idiopathic SE (Gross-Tsur and Shinnar, 1993). The classification of SE follows the classification of seizures (Gastaut, 1983).

In children, excluding neonates, generalized convulsive SE (GCSE) is the most frequent occurring type (Aicardi and Chevrie, 1970; Dulac et al, 1985; Vigevano et al, 1985). The greater part (50 - 75%) never had seizures before (table 1). The outcome of GCSE is especially determined by its cause. Outcome is worse in the acute symptomatic group in comparison with the idiopathic group or with patients with a chronic encephalopathy. Other factors of importance are age (Aicardi and Chevrie, 1970; Dulac et al, 1985) and duration of SE (Aicardi and Chevrie, 1970; Yager, 1988; Dunn, 1988; DeLorenzo et al, 1992). A significant contribution of duration with respect to outcome of SE was noted only in the acute symptomatic group (Maytal et al, 1989). A relationship between cause and mortality has been found especially in cases caused by tumours, but also by anoxia and metabolic problems (DeLorenzo et al, 1992). Fever alone, not associated with central nervous system infections was not associated with significant morbidity or mortality. Acidosis, glucose level or sex have no influence on outcome.

Generalized Nonconvulsive Status Epilepticus (GNSE) include typical absence SE and atypical absence SE; Encephalopathy related to Electrical Status Epilepticus during Sleep (ESES) or Epilepsy with Continuous Spike-Waves during slow wave Sleep (CSWS) and Landau-Kleffner syndrome (LKS) are syndromes occurring only in children. The international classification of epilepsies and syndromes has included both CSWS and LKS as syndromes undetermined whether focal or generalized. For practical reasons we have chosen to discuss both syndromes in relation to GNSE. GNSE may present severe diagnostic problems, especially in mentally retarded patients. EEG investigation is necessary and may show several epileptic EEG patterns.

Typical absence SE is relatively rare in children. Most are already known to suffer from idiopathic generalized epilepsy with absences and/or generalized tonic-clonic seizures, without any neurological impairment. Precipitating factors include infections (mostly respiratory), medication problems and stress. Duration does not exceed 24 hours in most cases. Apart

from complex partial SE, generalized NSE should also be distinguished from an acute confusional state caused by fever, trauma or metabolic problems (Amit, 1988), and from prolonged postictal encephalopathy (Biton et al, 1990).

CSWS was described for the first time in 1971 by Patry et al (1971); a more detailed description was published by Tassinari et al (1985). During CSWS severe mental deterioration may occur, together with behaviour disturbances. Recovery is possible, but considerable residual dysfunction has been reported (Jayakar and Seshia, 1991). Acquired epileptiform aphasia in children (Landau-Kleffner syndrome) is characterized by a progressive language disturbance that is most probably caused by epileptic discharges that occur especially during sleep (Deonna, 1991).

Partial elementary SE is rare in children and is in most cases (75%) somatomotor in expression. Consciousness is not impaired. When myoclonic jerks persist between the partial seizures, Epilepsia Partialis Continua is present (EPC). EPC is mainly limited to already neurologically impaired children (Bancaud et al, 1982).

Complex partial SE in children is recognized by impairment of consciousness, emotional or behavioural problems, lack of response to familiar persons, lip smacking, picking at nearby objects, focal clonic activity. EEG investigation is necessary, in order to distinguish it from absence SE. Complex partial SE may also occur in infants (McBride et al, 1981).

This study was prompted by the experience that in the different hospitals where the author worked rather divergent opinions about the care for status epilepticus (SE) were encountered. Furthermore, SE was generally considered a frightening condition implying an important association with mortality or at least morbidity, which did not seem to be corroborated in actual practice. First the literature was reviewed, next 112 cases of children admitted in a number of Dutch hospitals or treated in Special Centres for Epilepsy were collected and studied with respect to population characteristics, type of SE, causes, duration of the status, medical complications and strategy of therapeutic measures. Methods have been described in chapter 2.

Table 1: General characteristics of SE in children from the literature

	Aicardi 1970	Hayakawa 1979	Vigevano 1985	Yager 1988	Dunn 1988	Phillips 1989	Maytal 1989
Number	239	67	84	52	97	193	193
Duration of SE	>60	>60	>30	>30	>30	>30	>30
Age (yrs)	<15	<15	<13	<18	<18	<14	<18
Previous Epilepsy (%)	23	83	16	35	49	29	32
Causes (%)							
Acute symptomatic	26	16	42	30	15	43	23
Chronic encephalopathy	21	–	45	36	57	10	29
Idiopathic	52	–	13	32	28	46	48
Fever	28	–	6	21	16	32	24
Mortality (%)	11	3	6	6	7	6	3
Morbidity (%)	57	24	21	25	19	?	9

7.2 Results

In the Netherlands, with a population of about 15 million people, according to the SIG every year about 144 children are admitted because of SE (SIG, 1989). Most of these, i.e. 85%, are reported to have had generalized convulsive SE (GCSE). During our study of SE several hospitals in The Netherlands we found 112 children. One third had been admitted to the ICU (table 2).

The greater part (67%) was known with previous epilepsy. About half of the total group (54%) were mentally retarded. Of these, only 2 never had seizures before, and both presented with GCSE.

Generalized Convulsive SE (GCSE)

Most patients had GCSE (82), among them one with tonic and three with myoclonic SE. GCSE was strikingly asymmetrical in 33 patients.

The number of patients *with previous epilepsy* was 51; 41 were known with mental retardation. In patients with previous epilepsy a progressive neurological disease was considered responsible for convulsive SE in 5 cases:

Alpers disease (one), neuronal ceroidlipofucsinosis (one), mitochondrial encephalomyopathy (two), unknown cause (one).

The cause remained unknown in 23 patients. Precipitating factors were systemic infection in 16 cases (13 patients younger than 5 years), problems with anti-epileptic drugs in five patients and in one stress. In one patient a growing porencephalic cyst caused SE.

In 31 cases *without previous epilepsy* we found the following causes: acute symptomatic causes were present in 26 cases and consisted of viral encephalitis (herpes simplex in three, varicella in one, virus unknown in four), bacterial meningitis (pneumococcus in two), hypoxia (caused by respiratory infection in four), Rye-syndrome (one), metabolic disturbance (dehydration in one), toxic cause (CO in one, cytostatic drugs in one, carbamazepine in one, measles vaccination in one), cerebral contusion (four) and a space occupying lesion due to a ruptured AV-anomaly (one). In five cases febrile SE was present.

Table 2: Main characteristics of 112 children with SE

Age		6 months - 1 yr		1 – 5 yrs		5 - 15 yrs	
		Ward	IC	Ward	IC	Ward	IC
Male (54)		0	5	8	9	27	5
Female (58)		2	2	13	10	25	6
Epilepsy	Yes (75)	1	0	17	9	40	8
	No (37)	1	7	4	10	12	3
Mental Retardation	Yes (57)	0	0	13	8	32	4
	No (55)	2	7	8	11	20	7
GCSE (82)		2	7	18	19	27	9
NCSE (27)		0	0	3	0	22	2
EPSE (3)		0	0	0	0	3	0
Causes Previous epilepsy (75)							
Acute symptomatic		0	0	0	0	0	1
Medication problems		0	0	0	2	8	0
Systemic infections		0	0	9	6	1	2
Unknown		1	0	7	1	27	3
Progressive neurological disease		0	0	0	1	5	1
No previous epilepsy (37)							
Acute symptomatic		0	6	1	9	6	3
Remote symptomatic/Chronic encephalopathy		0	0	0	0	2	0
Unknown		0	0	1	0	3	1
Febrile		1	1	3	0	0	0

* When admission to the Intensive Care was necessary the patient is categorized IC; if not as ward. Epilepsy and mental retardation refer to the situation before the occurrence of SE

Non-Convulsive SE (NCSE)

NCSE consisted of CSWS in four patients, typical absence SE in only two (both initial), atypical absence SE in six and complex partial SE in 15 patients. This group of 15 patients was surprisingly large: in three the distinction with atypical absence was difficult, an EEG was not performed, all 3 were mentally retarded. The clinical presentation, however, was suggestive. In another eight patients the clinical distinction was obvious; in the remaining

four clinical presentation and EEG diagnosis were in accordance with the diagnosis of complex partial SE.

The two patients with typical absence SE were a boy and a girl with an age between 5 and 15 years. The cause of SE remained unknown. All cases with atypical absence SE had previously been diagnosed with epilepsy and mental retardation; five were between 5 - 15 years of age, only one between 1 - 5 years. The cause or precipitating factors remained unknown.

Most patients with complex partial SE (twelve) were known to have suffered previous epilepsy and eight with mental retardation. In cases without previous epilepsy (three) viral meningitis caused SE in one patient, in another patient a remote symptomatic cause was present (cerebral infarction); a systemic infection with fever was present in the third patient. Precipitating factors included medication problems in five.

Partial status epilepticus

The three patients with elementary partial SE (EPSE) were five, eight and twelve years of age; two were known to have epilepsy and a progressive neurological disorder of unknown origin. The third patient had EPSE because of a head trauma and never had seizures before.

Duration of SE

Duration of GCSE did not differ much in patients with or without pre-existing epilepsy (table 3). In five cases a succession of generalized convulsive seizures was present, without regaining consciousness, the exact duration was not documented.

In NCSE (excluding cases with CSWS) cases with a longer duration were more prevalent in patients with previous epilepsy in comparison to cases without previous epilepsy.

Duration of CSWS was more than 2 years in all four cases; duration of EPSE was weeks in two and 21 months in one patient.

Table 3: Duration of SE in cases without and with previous epilepsy*

Duration SE	No previous epilepsy (35)		Previous epilepsy (65)	
	GCSE	NCSE	GCSE	NCSE
< 2 hrs	17	3	26	5
2 - 8 hrs	7	2	9	4
> 8 hrs	6	0	12	9

* Absolute numbers. Excluded are cases with EPSE (3), CSWS (4) and 5 cases with inadequate documentation of seizure duration

Duration and outcome

Duration of GCSE appears very variable; the shorter the duration, the less the number of cases with sequelae or death. A brief duration (30 - 60 min.) accounts for 18% of morbidity (two cases) and 9% of mortality (one case). If duration is between 2 and 8 hours, 27% of morbidity and 18% of mortality is present. Duration of 8 hours or more accounts for half of the morbidity and 27% of mortality.

If one considers only cases in which the cause of morbidity or mortality can be directly attributed to SE and not to the underlying disease, then there is no morbidity prior to two hours duration and only one patient died. Again, only after more than 8 hours duration over half of the morbidity and mortality cases due to SE are encountered.

Cause and outcome

Overall outcome is worse in patients with an acute symptomatic cause (table 4). Acute symptomatic causes were more prevalent in children admitted to the Intensive Care Unit (60%) in comparison to those admitted to a regular ward (13%). Morbidity (10 out of 11) and mortality (all) occurred mainly in children admitted to the Intensive Care. The cause associated with the highest mortality was anoxia (all four died); in meningo-encephalitis morbidity was 40%, no one died. All cases with febrile SE or SE caused by head trauma had good outcome. Cases with a metabolic cause or space-occupying lesion had either morbidity or died, but the number of cases was low.

New neurological signs occurring during or after GCSE are presented in table 5.

In NCSE mental deterioration was obvious in two cases with CSWS. One patient developed complex partial status with a duration of hours because of a viral meningitis and complained of word findings problems that resolved in a period of 2 years. Whether this was due to the epileptic discharges or to an encephalitic lesion remains unknown. This patient was not known with previous epilepsy.

Table 4: Outcome of SE in children in relation to type of SE and cause*

	Good	Morbidity			Mortality		
		SE	Cause	Un-known	SE	Cause	Un-known
GCSE							
Acute symptomatic (31)	55	6.5	3.2	16.1	3.2	9.8	6.5
Previous epilepsy							
With MR (41)	85	2.4	4.9		7.3	0	
Without MR (10)	80	0	0	0	10	10	0
NCSE							
No previous epilepsy (5)	80	0	0	20	0	0	0
Previous epilepsy							
With MR (14)	85.7	14.3	0	0	0	0	0
Without MR (8)	100	0	0	0	0	0	0

* EPSE was excluded. Relative numbers (absolute numbers between brackets). MR= mental retardation

Table 5: Morbidity in convulsive SE*

New neurological signs	SE	Cause	Unknown
Persistent myoclonic jerks	0	2	1
Aphasia and blindness	1	0	0
Paresis of the arm	0	1	0
Cognitive problems/hemiparesis	0	0	1
Hemiparesis	1	0	1
Vegetative state	1	0	0
Other	0	0	2
Total	3	3	5

* Absolute numbers

Medical complications and outcome

Medical complications included respiratory insufficiency, hyperthermia, acidosis, hypotension, intracranial hypertension, and renal and hepatic failure. Outcome is worse in patients with 1 or more medical complications (table 6). Especially deleterious complications in children were respiratory insufficiency and intracranial hypertension. Medical complications occurred almost exclusively in convulsive SE, i.e. in 25 patients. The remaining two patients suffered from complex partial SE; outcome was good in both. In six children with GCSE intracranial pressure (ICP) was monitored; in one patient the results were normal. In five children, however, severe intracranial hypertension was present: three patients died (two because of SE, one because of underlying cause), two patients had new neurological problems. In two children the rise of the intracranial pressure was preceded by the start of an electro-encephalographic seizure.

Therapy and outcome

During our investigation we tried to establish the quality of the therapy of SE in relation to outcome. Insufficient therapy in GCSE may have contributed to outcome in 13% of the patients; this is not the case in NCSE (table 7).

Table 6: Outcome in children in relation to the presence of medical complications*

Medical complications	Outcome	Good	Morbidity	Mortality
No	70 (57)	88	9	3
1	12 (10)	80	20	0
>1	18 (15)	13	27	60

* No complications (no), one complication (1), more than one complication (>1). Relative numbers. (absolute numbers between brackets)

Table 7: Quality of therapy in relation to outcome*

Outcome	Good	Morbidity	Mortality
Therapy GCSE			
Good (59)	81,3	8,5	10,2
Insufficient (23)	52,2	26,1	21,7
Therapy NCSE			
Good (15)	93,3	6,7	0
Insufficient or none (8)	100	0	0

* Relative numbers. Absolute numbers between brackets. Exclusive CSWS (4) and EPSE (3).

7.3 Conclusions

The total number of 112 children with various types of SE from different types of hospitals (including 2 epilepsy centres) spread all over the country does permit us to investigate several questions with regard to SE in children, such as cause, therapy and outcome.

The greater part (82) had GCSE, especially tonic-clonic SE. We found causes and precipitating factors in agreement to other studies (Aicardi and Chevrie, 1970; Dulac et al, 1985; Vigevano et al, 1985; Yager, 1988; Dunn, 1988; DeLorenzo et al, 1992). Our group however showed a higher percentage of previous epilepsy and mental retardation.

The younger age group showed relatively more cases with acute symptomatic causes; the younger the age, the worse the outcome: in children less than one year outcome is good in three out of nine (33%), in children 1 - 5 years in 29 out of 40 (72.5%) and in children 5 - 15 years in 53 out of 63 (84%). The cause is the main determinant with respect to outcome, not age. This agrees with the finding that outcome is worse when admitted to the Intensive Care and by the fact that the percentage acute symptomatic causes in patients admitted to the Intensive Care is higher than in patients admitted to a regular ward. Causes associated with poor outcome are brain tumours, anoxia and metabolic problems (DeLorenzo et al, 1992). We confirmed this especially with regard to anoxia.

The relation between outcome and duration had been investigated also by others (Aicardi and Chevrie, 1970;Yager, 1988; Dunn, 1988; Maytal et

al, 1989; DeLorenzo et al, 1992). In our group we found that outcome in convulsive SE was worse when duration exceeds 8 hours; when we consider only cases with SE as the sole determinant for outcome we found that a duration of more than two hours already contributed to a worse outcome. Duration of SE did not depend on the cause. In cases of NCSE duration was generally longer.

Outcome in NCSE was favourable in most cases; mental deterioration in CSWS is part of the syndrome and the word findings problems after CPSE in a patient with viral meningitis were temporary. The number of cases with CPSE (fifteen) stresses the fact that CPSE occurs more frequently than acknowledged until now.

The low number of cases with EPSE makes it difficult to draw conclusions. That is why we only mention the main features we found in these 3 patients.

The relation between medical complications and outcome in children has not been reported before in the literature. Experimental results in animals have stressed the importance of adequate treatment of the medical complications occurring during the course of GCSE (Meldrum, 1983; Siesjo and Wieloch, 1986). According to the literature in adults the degree of metabolic acidosis did not correlate with outcome, hyperthermia caused a worse outcome (Aminoff and Simon, 1980). In accordance with the results in 346 adult patients with GCSE (Scholtes et al, 1994) we found that outcome in children with GCGE is worse with one or more medical complications. Especially intracranial hypertension appeared to be a significant negative factor. In cases with difficult to treat SE and medical complications, intracranial pressure should be monitored, also because epileptic discharges appeared to cause a rise of intracranial pressure in two of our patients. A corresponding relation between intracranial pressure and epileptic discharges has been found by others (Tsementzis et al, 1979; Gabor et al, 1983) and in one of our adult patients.

The quality of therapy was questionable in 23 cases of GCSE and in 8 cases of NCSE. Especially in the convulsive cases this may have contributed to outcome. When insufficient, outcome was good in only 12 of the 23 cases (52%), whereas in cases of good therapy outcome was good in 81%. In cases of insufficient therapy morbidity was 26% (in cases of good therapy 8.5%) and mortality 22% (versus 10.2% in cases of good therapy).

Therapy should be prompt and according to a protocol, including a time schedule, to prevent unnecessary delay. Together with an adequate choice of the anti-epileptic drug and prevention of medical complications this may contribute to a more favourable outcome for children with SE (Scholtes et al, 1993).

Chapter 8

Cognitive Deterioration and Electrical Status Epilepticus during Slow Sleep

Epilepsy & Behavior 2005; 6: 167-173.

Summary
The results of long-term follow-up of 10 children with global or specific cognitive deterioration and on the electroencephalogram an electrical status epilepticus during sleep (ESES) are presented. They have been referred because of cognitive deterioration and underwent repeated neurological and neuropsychological examinations and all-night electroencephalography (EEG). A previous cognitive level was known or could be estimated in all. A Continuous Spikes and Waves during Sleep (CSWS) syndrome was present in 7 children, with global cognitive deterioration in 4 and more specific cognitive decline in 3, and a Landau-Kleffner syndrome (LKS) in another 3 children. Two children never had seizures, while the other had localisation-related epilepsy. No children had aggravation of clinical seizures. However, therapy was disappointing. Cognitive dysfunction did not respond to valproate and/or benzodiazepines in nine of the ten children. A relation with a frontal epileptic focus could be found in 5 of 7 children with CSWS, and with a left temporal focus in 2 of 3 children with LKS. The ESES persisted in CSWS during 5-9 years and in LKS during 1-5 years, and disappeared at puberty. Good cognitive recovery after disappearance of ESES occurred in only one child, partial recovery in four. Unfavourable prognosis of cognitive deterioration seems related to the long duration of the ESES and/or early onset of the epileptic activity. The authors are of the opinion that cognitive deterioration in children, with or without manifest epileptic seizures, should imply EEG investigation during sleep.

8.1 Introduction

Electrical Status Epilepticus during Sleep (ESES) consists of sleep-induced continuous paroxysmal discharges of spike-wave (SW) complexes with a frequency of 1.5-3.5 Hz on the electroencephalogram (EEG). ESES may appear continuously or discontinuously during sleep and is usually diffuse and bilateral. ESES can last several months or years and typically occurs during an important developmental period of childhood, between the age of 3 and 14 years. ESES can be found in several childhood epileptic conditions, but has its most peculiar expression in two specific age-related and self-limited disorders, recognized by the Commission on the Classification and Terminology of Seizures of the International League against Epilepsy

(ILAE): the Continuous Spikes and Waves during Sleep (CSWS) and the acquired epileptic aphasia or Landau-Kleffner syndrome (LKS). CSWS was first described by Patry et al (1971) as a subclinical "electrical status epilepticus" induced by sleep in children. They described six children with epilepsy and cognitive regression, whose EEG during sleep showed a pattern of continuous electrical status epilepticus (Patry et al, 1971). Later they introduced the neurophysiological term "electrical status epilepticus during sleep" (ESES) (Tassinari et al, 1977). In 1983 the acronym CSWS was reserved to describe the clinical condition and ESES for the associated nocturnal EEG abnormality (Billard et al, 1990; Jayakar and Seshia, 1991; Tassinari et al, 1992; Bureau, 1995; Roussele and Revol, 1995; Smith, 1997; Veggiotti et al, 1999).

Landau and Kleffner described in 1957 an acquired aphasia in six children with a convulsive disorder (the Landau and Kleffner Syndrome, LKS) (Landau and Kleffner, 1957). LKS is a severe, partly reversible, age-related childhood clinical syndrome, characterized by verbal auditory agnosia, quickly followed by a regression of spontaneous speech, in 3 of 4 cases seizures and behavioural disorders, and in all cases a sleepEEG which is similar in many ways to that in CSWS (Landau and Kleffner, 1957; Hirsch et al, 1990; Paquier et al, 1992; Deonna and Roulet, 1995; Smith, 1997).

There are also occasional reports of children with ESES and other specific cognitive disorders, such as dyspraxia and non-verbal learning disorders, specific attention disorders and acquired opercular syndrome (Billard et al, 1994; Motte et al, 1994; Shafrir and Prensky, 1995).

It is well accepted that epileptiform activity can cause cognitive and behavioural disorders. A more or less direct time link exists between cognitive disturbances and the diffuse or focal epileptiform abnormalities. Even brief discharges of a few seconds, without clearly perceptible clinical symptoms, so-called subclinical discharges, can result in cognitive dysfunction, known as transient cognitive impairment (Aarts et al, 1984). In CSWS, there are several indications that a relationship exists between continuous nocturnal discharges and a regression in cognitive functioning and/or behavioural problems (Billard et al, 1990; Tassinari et al, 1992; Smith, 1997; Veggiotti et al, 1999). However, scientific research is faced with a number of methodological problems. First, the clinical phenomenology is ill defined. Second, children with CSWS are only sporadically neuropsychological examined before onset

of the syndrome, which makes conclusions about regression sometimes problematic. Third, there are major differences in the psychological tests that have been used. In many cases, only the intellectual level is examined and not other cognitive functions, such as language, attention and memory. Moreover, there is insufficient conformity in the employed tests. Despite these methodological restrictions, a syndrome description does seem possible (Jayakar and Seshia, 1991; Roulet et al, 1991; Roussele and Revol, 1995; Morrell, 1995).

Over the past 10 years, we treated and followed ten children with cognitive deterioration, behavioural problems and a sleep-EEG that showed continuous epileptic activity; two children never had clinical seizures. The same protocol for examination and treatment was applied in all ten children. The results of long-term follow-up of these children are presented and discussed in relation to the literature.

8.2 Methods

All children referred to our clinic because of cognitive deterioration underwent a diagnostic protocol, including evaluation of the clinical history, physical examination, standard EEG and whole night sleep-EEG registration, neuropsychological examination, and neuro-imaging (MRI or CT-scan).

The degree of epileptic activity during sleep was measured and expressed in an index, which was defined by the total duration of continuous epileptic (diffuse slow SW) activity in relation to the total slow sleep duration with the exception of the REM-phase. The term ESES has been used when the index was 85% or more, according to Tassinari et al (1977). CSWS was diagnosed when there was a global or specific cognitive deterioration and LKS when there was speech deterioration (acquired aphasia) due to a verbal agnosia, in both conditions together with ESES. All patients underwent neuropsychological tests, in order to assess their general intellectual functioning, language functions, attention and concentration, memory functions and visual spatial abilities. The selection of tests used was dependent on patient's factors such as age and general mental abilities. During the follow-up, sleep-EEG and neuropsychological examination were repeated at least twice.

8.3 Results

The main characteristics of the children in our study are listed in the table I-a and I-b.

In all children, other causes of cognitive deterioration, except ESES, have been excluded.

Seven children fulfilled the criteria of CSWS, 4 patients (patient 1-3 and 5) had a global cognitive deterioration and 3 (patient 4, 6, 7) had a more specific cognitive decline. LKS was diagnosed in 3 children (patient 8-10). Pre-existent cognitive levels, determined by neuropsychological investigations, were known in 4 CSWS children, in the other 3 CSWS and 3 LKS cases the cognitive levels could be estimated based on the performances at school. In all children cognitive functioning was better before than during the CSWS or LKS period.

Patients 1, 2 and 5 showed typical ESES, associated global deterioration and severe behavioural problems. Despite the same EEG pattern, patient 3 presented a less severe clinical picture. Patients 4, 6 and 7 had ESES, more specific cognitive impairment and behavioural problems. Patient 4 manifested a relatively great language dysfunction in the beginning of the CSWS, but the verbal disability was not verbal agnosia, typical for LKS. Patient 6 showed regression of non-verbal functions, with severe impairment of visual-spatial tests. Her profile fits with a non-verbal learning disorder (NLD). This was also true, but to a lesser degree, for patient 7. The clinical presentation of patients 8, 9 and 10 matches that of LKS. However, these three children did not present behavioural problems.

Birth was eventful in eight of the children: breech birth in two, vacuum extraction in two, forceps in two, caesarean section in one, and premature birth in one. Pre-existent brain damage (meningitis, cerebral haemorrhage, hydrocephalus) was mentioned in the medical history of four children, all with CSWS. A previous cognitive deficit was present in none of the CSWS or LKS children. CT-scan was normal in three patients (patient 1, 4, 10) and MRI in two (patient 6 and 8). In one patient with LKS neuro-imaging had not been performed. MRI showed discrete atrophy of the right frontal area in patient 2, CT showed underdevelopment of the right hemisphere and a hypodensity of the right parietal lobe in patient 3, a hydrocephalus in patient 5, and hypodensity of the right frontoparietal region in patient 7.

The diagnosis epilepsy was made at an age of 2½ to 7 years, with the exception of patients 5 and 8, who never had epileptic seizures. All children with seizures had partial epilepsy, with complex partial seizures (patient 1, 4, 9, 10), secondary generalized tonic-clonic seizures (patient 2, 3), or partial motor seizures (patient 7); patient 6 had atonic seizures and myoclonic jerks. Two patients even had partial status epilepticus. Tonic seizures were not observed. In all children with seizures the EEG before the start of CSWS or LKS showed focal abnormalities. During the clinical course of CSWS and LKS the epileptic seizures did not grew worse; the seizure frequency was daily in patient 4, but only sporadic or zero in the other children.

After the disappearance of the nocturnal ESES pattern at puberty (ages 13 to 14 years), seizures persisted in patient 4 (sporadically nocturnal seizures) and in patient 6 (monthly nocturnal seizures).

CSWS with global deterioration showed a frontal focus in two patients (patient 2 and 3) and maximal epileptic activity in the left hemisphere in the other two (patient 1 and 5). The patient with a relatively greater language regression (patient 4) showed a preferred left frontocentral localisation. Patient 6 with the NLD-profile usually had maximum epileptic activity over the right frontocentral and to a lesser extent left frontal region. Patient 7 with also a NLD-profile showed a right frontal focus. In two LKS children (patient 8 and 9) a left (fronto-) temporal focus was reported. In the third LKS child (patient 10) a maximal epileptic activity over the right fronto-central region was noted.

Age at diagnosis of CSWS varied from 5.9 to 13 years, age at diagnosis of LKS from 4.6-6.6 years. In eight children (patient 1, 2, 5-10) there was moderate to serious cognitive regression, in two this was less pronounced (3, 4). The two children who were older at the time of diagnosis of CSWS (13 and 10 years) had no or only slight behaviour disturbance and only slight cognitive regression (patient 3 and 4). Behaviour problems in the seven children with CSWS were severe in five, slight in one and absent in one. Severe behaviour problems consisted of hyperkinetic disorder, attention deficit, and oppositional and aggressive behaviour. Patient 4 with slight behaviour problems had periodic outbursts of anger. Behaviour problems were absent in the three cases with LKS. All cases with severe cognitive regression showed severe behaviour problems. The main epileptic focus was frontal in three of five CSWS children with severe behaviour problems.

The duration of the ESES pattern in the CSWS patients was 5-9 years and in the LKS patients 1-5 years. Cognitive recovery was complete in only one patient (patient 4) and partial in four patients (2, 3, 8 and 10); five patients (1, 5, 6, 7 and 9) showed no recovery. No clear link could be established between the degree of recovery and the duration of the CSWS pattern. Behavioural disturbances disappeared after resolution of the ESES pattern in all, although patient 4 continued to have social problems.

The ultimate goal of treatment of CSWS and LKS is the disappearance of the ESES pattern, which is supposed to be the cause of cognitive regression. The effect of first line anti-epileptic drugs (AEDs), valproate and benzodiazepines, was disappointing in 9 of 10 children; only patient 9 reacted favourably to valproate. A few children even showed an adverse behavioural reaction (patients 2, 4 and 5). A more aggressive therapy has been applied in patients 6-8. Patients 6 and 7 have been prescribed all currently accepted AEDs in cases of ESES (valproate, benzodiazepines, lamotrigine), but also corticosteroids and intravenous immunoglobulines. No patients were surgery candidates. The duration of CSWS was the shortest (4 years) in patient 6, but had no positive effect on cognition, while patient 8, with duration of ESES of 1 year, had a good cognitive recovery.

8.4 Discussion

The aetiology and pathophysiological mechanisms of the age-related syndromes CSWS and LKS are unclear. An (auto) immunological mechanism has been suggested in cases responding to corticosteroids or immunoglobulins. Many researchers consider the prolonged nocturnal epileptic discharges to be responsible for the specific or overall cognitive deterioration. It is known that neurological damage can occur as a result of generalised convulsive status epilepticus and memory disorders after complex partial status epilepticus, corresponding to the area of maximum epileptic activity (Nevander et al, 1985; Engel et al, 1978). In the non-convulsive generalised status epilepticus or absence status, no neurological deficit has been described. On the contrary, if the ESES pattern during sleep disappears after years, spontaneously or under the influence of AEDs, cognitive functioning and behaviour may improve, but complete recovery is rare (Roulet et al, 1991; Maresceaux et al, 1990; Yasuhara et al, 1991).

The degree of maturation of the cortical network of the brain is high between the ages of 1 to 8 years. Disturbances taking place during this period may result in permanent impairment of this network. The earlier the epileptic disturbance occurs, the greater the functional deficit. The type of functional deficit is dependent of the area in which this epileptic activity is concentrated. In most of the CSWS patients this is the frontal region (Kobayashi et al, 1988; Tassinari, 1995), and in LKS patients the temporal lobe (Morrell, 1995; Paetau et al, 1999). Over time this dysfunction can spread across a wider area of the brain and give rise to other disabilities. Because the epileptic activity is bilateral, the disturbed function cannot be taken over by the contra lateral homotopic cortex (Smith, 1997).

In none of the children in this study a specific cause could be found, but in all the severe nocturnal EEG abnormalities give a plausible explanation for the cognitive regression. Eight patients had localised epilepsy and two, without epileptic seizures, an asymmetrical EEG. In all the children the sleep-EEG normalised at puberty. A preference for frontal epileptic discharges in CSWS and for left temporal discharges in LKS could be confirmed in our study. In one of the LKS children nocturnal continuous epileptic activity was more pronounced over both occipital regions. Our CSWS patients showed global deterioration in four cases; one patient showed a relatively greater language dysfunction, but not corresponding to typical LKS. Two children showed regression of non-verbal functions, with severe impairment on visual-spatial tests. Both showed a main right frontal focus of epileptic activity, which is in agreement with the supposed pathogenesis of this syndrome.

Some researchers have suggested a possible role for cerebral pathology, such as a cerebral tumour or inflammation (Perniola et al, 1993; Solomon et al, 1993; De Volder et al, 1994). According to the literature, approximately 25% of the CSWS children have evidence of a pre-existent brain damage, caused for example by a meningitis or birth trauma, and 30% have an abnormal cerebral CT or MRI scan (Billard et al, 1990; Jayakar and Seshia, 1991; Tassinari et al, 1992; Bureau, 1995; Roussele and Revol, 1995; Smith, 1997; Veggiotti et al, 1999), while in 75% of the CSWS children no previous cognitive handicap or behavioural problem is mentioned. Most LKS children are initially normal and achieved developmental milestones, including speech, at appropriate ages. Cerebral CT or MRI usually shows

no abnormalities (Landau and Kleffner, 1957; Hirsch et al, 1990; Paquier et al, 1992; Deonna and Roulet, 1995; Smith, 1997). Neuropathological examination in LKS has not revealed abnormalities until now (Cole et al, 1988; Smith et al, 1992). In our patient group, it was striking that the number of children with perinatal problems was high (8 of 10 cases). Perhaps this was due to the systematic questioning on the perinatal condition. Neuroimaging was normal in two LKS children and three CSWS children, while in the other four CSWS children only minor non-specific abnormalities were found.

The age at onset of CSWS and LKS and the *observed seizure types* in our children are in accordance with data reported in the literature (Landau and Kleffner, 1957; Billard et al, 1990; Jayakar and Seshia, 1991; Paquier et al, 1992; Tassinari et al, 1992; Bureau, 1995; Roussele and Revol, 1995; Deonna and Roulet, 1995; Smith, 1997; Veggiotti et al, 1999; Robinson et al, 2001). The average age at onset of five cases with CSWS was 7.1 years (from 3 to 9). Two other cases with CSWS had a relative late onset at 10 and 13 years, with no or only slight cognitive decline or behaviour disturbances. Outcome in these two children was, despite a long duration of ESES (6 and 9 years), favourable. The age at onset in the three LKS children was 4.6-6.6 years. Clinical seizures are not obligatory signs for the diagnosis CSWS or LKS. Two children in our group never had seizures. It has been reported that, when CSWS children show cognitive regression, seizures may become more frequent (Tassinari et al, 1992); in LKS, seizures are infrequent and respond well to therapy. In our group most children had only sporadic or even no seizures.

The duration of ESES and cognitive outcome seem correlated. Duration of ESES in CSWS varies from a few months to several years (Bureau, 1995). In one third of the patients, despite the disappearance of ESES, epilepsy persists after puberty. In half of the patients cognition does not ameliorate. The prognosis is better in patients with a shorter CSWS duration (Dalla Bernardina et al, 1989; Bureau et al, 1990) and cognitive deterioration is less when the age at onset of CSWS is after the age of 8-9 years. A direct correlation with the severity of the epilepsy has not been proven, nor could the presence or absence of a cerebral lesion or the age at which the diagnosis CSWS is made be related to the prognosis (Tassinari et al, 1992). In LKS,

the mean duration of ESES is from 12 to 96 months (32). Language and other neuropsychological dysfunctions gradually improve parallel with the disappearance of ESES. Prognosis concerning verbal recovery is favourable in 30% of the children. The others show only partial or no recovery. Prognosis is worst in children with a long duration of ESES and in children in whom the treatment was delayed (Grote et al, 1999; Irwin et al, 2001). No LKS child with a duration of ESES of more than 3 years had normal language outcome (Robinson et al, 2001). This is perhaps the reason that children with later onset of LKS (or shorter ESES duration) have in general a better outcome (Gerard et al, 1993).

In our study, all CSWS and LKS children had an ESES index of 80% or more. Duration of the ESES pattern in our CSWS group varied from 4.1 to 9 years, without any correlation with cognitive outcome. Outcome in our CSWS and LKS children was poor, but the duration of CSWS was relatively long. Prognosis was better when the age of onset was over 9 years. One LKS child recovered completely and had the shortest ESES period (1 year), also one CSWS child had a good outcome, despite a lengthy ESES duration (6 years). This child had an age at onset of 10 years, which may have been important in this respect. One child with CSWS made a partial cognitive recovery; it also was relatively old at onset (13 years) but had a lengthy ESES duration (9 years). The two children with LKS and partial recovery had ESES duration of 4.5-4.9 years, which is probably too long for complete language recovery (Robinson et al, 2001). In one patient with LKS persistent impaired auditive memory was noted after partial recovery of the language function. This has also been reported in two studies with larger groups of LKS patients (Robinson et al, 2001; Grote et al, 1999).

Behavioural problems with attention deficit, hyperkinesia, aggression, impulsivity and lack of inhibition are often present in CSWS (Billard et al, 1990; Jayakar and Seshia, 1991; Tassinari et al, 1992; Bureau, 1995; Roussele and Revol, 1995; Smith, 1997; Veggiotti et al, 1999) and in LKS (Landau and Kleffner, 1957; Hirsch et al, 1990; Paquier et al, 1992; Deonna and Roulet, 1995; Smith, 1997). A relation with frontotemporal EEG abnormalities has been suggested (Robinson et al, 2001).

Behaviour disturbances in our CSWS children were corresponding to those reported in the literature. Behaviour normalised after disappearance of the ESES pattern, even after long-standing ESES; normalisation was not correlated to restoration of cognition. In contrast to most patients described with LKS, our three LKS children did not show behaviour problems, despite the presence of frontal EEG abnormalities in two of them.

Treatment with valproate and/or benzodiazepines is the first choice and may have a positive effect on CSWS (Smith, 1997; Yasuhara et al, 1991). Incidental positive results have been reported with corticosteroids, ACTH, ethosuximide, clomipramine and amphetamine (Billard et al, 1990; Maresceaux et al, 1990). Negative results, or even deterioration, have been reported with carbamazepine, phenytoin, and phenobarbital (Boel et al, 1989; Maresceaux et al, 1990; Veggiotti et al, 1999). Seizures in LKS are in general responsive to standard AED therapy. In some cases valproate, ethosuximide, benzodiazepines and corticosteroids have some positive effects on ESES and aphasia, but not always permanent (De Marco, 1988; Maresceaux et al, 1990; Lerman et al, 1991; Yalcin et al, 1995; Aykut-Bingol et al, 1996; Robinson et al, 2001). Incidental positive results have been reported with felbamate, nicardipine-nimodipine, sulthiam and intravenous treatment with immunoglobulins (Pascual-Castroviejo et al, 1992; Glauser et al, 1995; Fayad et al, 1997; Lagae et al, 1998). Carbamazepine and phenytoin have adverse and phenobarbital no effect on aphasia (Maresceaux et al, 1990). Some children with LKS have been successfully treated with multiple subpial transections (Morrell, 1995; Sawhney et al, 1995; Irwin et al, 2001). The results of therapy on cognitive functions in our group of patients with the first choice AEDs were disappointing. Only one case with LKS and a relatively short ESES duration reacted favourably to corticosteroids.

Based on the literature and our results, it is obvious that children with CSWS or LKS should be treated according to a protocol. Special attention should be given to a narrow time schedule, in order to prevent permanent deficit (Dalla Bernardina et al, 1989; Bureau et al, 1990; Grote et al, 1999; Robinson et al, 2001). If the condition is not recognised or is neglected, it may result in irreversible cognitive regression and behaviour problems. In any child with unexplained cognitive regression, the following tests

should be performed: EEG registration during sleep (entire night), neuropsychological examination, and paediatric-neurological examination; other possible causes of ESES should be excluded. The treatment of CSWS and LKS is complex, because of medical and psychological problems. Therefore, best results can be achieved by a multidisciplinary approach.

Once the diagnosis has been made, treatment should start as soon as possible, taking as a guideline a protocol in which, apart from medication, attention is given to the behavioural problems, adequate counselling and parent guidance. If first choice drugs (valproate and/or benzodiazepines, such as clonazepam or clobazam) fail, start with corticosteroids but be alert to possible hormonal side effects. When the results are disappointing, consider intravenous immunoglobulins. Neurosurgery (subpial transsection) in specialised centres has been proposed within three years after the start of the cognitive regression (Irwin et al, 2001). Given the relatively low incidence of this condition, pooling of experience and knowledge is important. Treatment should preferably be given on an outpatient basis, with support and guidance for the caregivers of the child. In exceptional cases the behavioural problems can be so severe that a clinical setting with child psychiatry expertise is necessary.

Table 1a: Main characteristics of children with global cognitive deterioration and ESES. Patient 1-5: CSWS with global cognitive deterioration

Patient	1	2	3	4	5
Previous history	Breech birth	Meningitis	Vacuum extraction, Intra-cranial haemorrhage	Vacuum extraction	Forceps, meningitis hydrocephalus
Onset epilepsy	4 years	4,10 years	5 years	7 years	None
Type epilepsy	Partial	Partial	Partial	Partial	None
Diagnosis CSWS	6,6 years	7,5 years	13 years	10 years	9 years
Behavioural problems	Severe	Severe	None	Slight	Severe
Cognitive regression	Severe	Severe	Slight	Slight	Moderate
Cognitive recovery	None	Partial	Partial	Complete	None
Behavioural recovery	Good	Good	Good	Good	Good
Maximum epileptic activity	Left hemisphere	Left frontal	Right frontal	Left parieto-temporal	Left hemisphere
Duration ESES	6,6 years	6,4 years	9 years	6 years	5 years

Table 1b: Main characteristics of children with specific cognitive deterioration and ESES*

Patient	6	7	8	9	10
Previous history	Caesarean section	Premature, hydrocephalus Intra-cranial haemorrhage	Forceps, foetal distress	Breech birth	Unremarkable
Onset epilepsy	2,6 years	4,6 years	None	4 years	5 years
Type epilepsy	Partial	Partial	None	Partial	Partial
diagnosis CSWS/LKS	6,6 years	5,9 years	5 years	4,6 years	6,6 years
Behavioural problems	Severe	Severe	None	None	None
Cognitive regression	Severe	Severe	Verbal severe	Verbal severe	Verbal severe
Cognitive recovery	None	None	Partial	Partial	Partial
Behavioural recovery	Good	Good	N/a	N/a	N/a
Maximum epileptic activity	Right fronto-central, Left frontal	Right frontal	Left fronto-temporal	Left temporal	Right Fronto-central
Duration ESES	4,2 years	4,1 years	1 year	4,9 years	4,5 years

*Patient 6-7: CSWS with specific cognitive deterioration; Patient 8-10: LKS. N/a=not applicable.

Addendum: clinical case histories CSWS and LKS

Patient 1: This boy was born in 1982. He developed normally during his first years. The onset of epilepsy occurred at the age of 4 years. He developed sporadically occurring complex partial seizures with a favourable reaction to valproate. At the age of 6½ years he was evaluated in our centre because of learning and behavioural disturbances. The diurnal EEG showed diffuse spike and poly-spike wave activity in short and long series, maximal above the left hemisphere. EEG during sleep showed, with the exception of the REM phase, continuous spike wave (SW) activity with a frequency of 1.5-3.5/sec, left more clearly than right. The SW index was more than 85%. Psychological examination revealed a diffuse cognitive dysfunction with a total IQ of 85. Comprehensive metabolic examination revealed no abnormalities; CT-scan was normal. Benzodiazepines (clobazam, lorazepam) proved ineffective and aggravated the behavioural problems. At the age of 8 years the behavioural problems increased. His cognitive level had meanwhile further regressed to a total IQ of 59. Ethosuximide brought a slight improvement to the EEG during sleep pattern, but had no influence on the clinical picture. With lamotrigine the nocturnal epileptic activity decreased from continuous to approximately half of the sleep period. The clinical picture continued to be characterised however by serious behavioural problems, nor was there any cognitive improvement. By the age of 13 years the EEG pattern was almost completely normalised; during the night only sporadic epileptic activity. The behaviour problems disappeared completely. His learning skills had improved slightly, but his intellectual level remained unchanged (total IQ 60).

Patient 2: This girl was born in 1982. As newborn baby she had meningitis, caused by a haemolytic streptococcus. At the age of 4 years and 10 months she had a first tonic-clonic seizure with convulsions primarily in the left half of the body. A CAT scan was normal. The EEG revealed left parietal local spike wave activity with spreading to the central, occipital and temporal areas. She was prescribed fenytoin. Because of concentration disturbances fenytoin was replaced by valproate at the age of 6 years and 6 months. This now caused substantial behavioural problems. Carbamazepine was prescribed. One month later she had a tonic-clonic seizure of ten minutes followed by hours of reduced awareness, with attendant automatisms. With

these symptoms she was hospitalised elsewhere. The EEG at that moment showed a seriously disturbed pattern with many bilateral synchronous spike wave series. Acetazolamide had no effect, ethosuximide aggravated behavioral problems. The patient was subsequently admitted to our clinic. At this time the EEG showed continuous spike wave activity with a frequency of 2 to 2½ Hz, both diurnal and nocturnal, which had a preference for left frontal. Diazepam reduced this spike wave activity. With the stopping of carbamazepine this pattern of continuous spike wave activity disappeared, although there was still some diffuse epileptic activity. Neuropsychological examination revealed a low-average level. For some time the patient did quite well without medication, but then at the age of 7 years and 5 months she had another tonic-clonic seizure, followed by increasing behavioural disorders, decreasing school performance and poor memory recall. The diurnal EEG again showed much bilateral spike wave activity from 2 to 3 Hz with series of up to ten seconds. This activity was continuously present during sleep, with the exception of the REM phase. The SW index was greater than 85%. Comprehensive metabolic examination, CAT scan, skin sample, Evoked Potentials and an EMG revealed no abnormalities. Benzodiazepines had no effect, valproate and barbiturates aggravated the behavioural problems. Her cognitive level had meanwhile regressed to a total IQ of 42. In the light of her adverse reaction to various anti-epileptic drugs, it was decided to discontinue medication. Over the subsequent years the clinical picture slowly improved. At the age of 13 years and 9 months nothing exceptional was to be seen on either the diurnal or the nocturnal EEG. She was at that time attending a Jena plan school and showing an improvement in her scholastic skills. Except for the Rickham reservoir and some atrophy right frontal, the MRI revealed nothing unusual.

Patient 3: This boy was born in 1973 by vacuum extraction. At the age of four days he had fits with cyanosis and apnoea. At the same time a hemiparesis left developed. The cause was an intra-cranial haemorrhage. At the age of 2 years he was walking and speech was also progressing nicely. At the age of 5 years he had a first tonic-clonic seizure. He was prescribed valproate and carbamazepine. He subsequently had approximately one major seizure per year and also had occasional `absences'. At primary school he was an average pupil until the age of 10 years. His development then

stagnated and he was placed in a school with special assistance. At the age of 13 years he was evaluated in our centre because of learning disturbances. The diurnal EEG was asymmetric to the disadvantage of the right without specific abnormalities. During sleep however there was continuous spike wave activity of 2 Hz, with a maximum right frontal, with the exception of the REM phase. Neuropsychological examination revealed a verbal IQ of 59 and a non-verbal IQ of 63. Treatment with benzodiazepines had no effect. Discontinuation of anti-epileptic drugs made him much more alert. At the age of 22 years the epileptic activity appeared to have completely disappeared. He is now taking driving lessons and functions adequately as a gardener at a sheltered workplace.

Patient 4: This girl was born in 1978 by vacuum extraction. At the age of 1 year she had a first non-febrile tonic-clonic seizure. No medication was given. At the age of 7 years she presented a complex partial status epilepticus of several hours with reduced awareness, tonic cramps, right more than left, and confusion. A CT-scan was normal. The EEG showed epileptic activity left parieto-temporal. There was a high-average level of intelligence with a relative language deficit. Anti-epileptic drugs prescribed included fenytoin, carbamazepine and valproate in combination with ethosuximide. At the age of 10 years she was evaluated in our centre in connection with outbursts of anger and increase of the seizures accompanied by blank staring and automatisms. The EEG showed local epileptic activity left fronto-central. When the ethosuximide was stopped her behaviour improved markedly. She did however continue to have daily seizures. An EEG during sleep showed continuous bilateral spike wave activity, with the exception of the REM phase; there was less epileptic activity in the right-posterior area. The SW index was more than 85%. Apart from valproate, she was prescribed benzodiazepines. These proved to have no effect. Her scholastic skills declined and her intelligence level dropped to low-average (IQ of 86). At the age of 16 years the EEG normalised and the diurnal absences stopped. Her intellectual ability restored itself to an average level (IQ of 105), she did however continue to have social problems and sporadic nocturnal attacks.

Patient 5: This girl was born in 1979 by forceps extraction. At the age of seven weeks she developed a streptococcus meningitis. In connection with a hydrocephalus, she was given a drain. Her development was slightly

retarded and until her 4th year she was prescribed prophylactic fenytoin. At the age of 6 and 8½ years there was a drain dysfunction. She was again prescribed prophylactic an anti-epileptic drug, this time valproate. At the age of 7 years she had a low-average level of intelligence with a total IQ of 90. In connection with behavioural problems and difficulties at school, further examination in our centre followed at the age of 9 years. By means of psychological examination a total IQ of 60 was now determined. The diurnal EEG showed paroxysms of spike wave activity in the left hemisphere. During sleep diffuse, left predominantly continuous epileptic activity was seen with the exception of the REM phase. The SW index was more than 85%. The diagnosis CSWS was made. When the valproate was stopped the behavioural disorders disappeared. By her 14th year the EEG pattern, both diurnally and nocturnally, had more or less normalised. Her cognitive ability however had only marginally improved (total IQ 72).

Patient 6: This girl was born in 1987 by caesarean section. Development was normal. At the age of eight months she had a febrile convulsion. At 2½ years she also began to have non-febrile seizures and later also myoclonia and atonic seizures. She was put on valproate, to which she reacted favourably until her 5th year, when she developed status epilepticus with myoclonia, reacting poorly to anti-epileptic drugs. During her 7th year cognitive regression became apparent. Further psychological examination revealed a performance decline. At the age of 4 years her IQ was 125, at the age of 7 years it was 86, with a verbal IQ of 95 and a non-verbal IQ of 78. At the age of 9 years her IQ had further declined to 63, verbal 77 and non-verbal 55. An EEG at the age of 6 years did not yet reveal a CSWS picture pattern. Half a year later however there was a nocturnal pattern of continuous epileptic activity, especially right centro-frontal and to a lesser extent left frontal. The SW index was more than 85%. Various anti-epileptic drugs were without effect. Corticosteroid therapy (prednisone) had a positive effect on her cognitive functioning, but unfortunately this turned out to be temporary; after discontinuation the situation deteriorated. A second course of prednisone again had a reasonably positive effect on her epilepsy and cognitive functioning. Compulsive eating turned out to be a great problem. When she was on prednisone, the EEG during sleep showed a marked improvement. This once again deteriorated when the

prednisone was discontinued. Further metabolic examination and magnetic resonance imaging (MRI) showed no abnormalities. In connection with the seriousness of the clinical picture, it was mutually agreed to determine whether the patient was eligible for surgical treatment (multiple subpial transection). Further examination revealed however that there were at least two independent epileptic foci, right fronto-central and left frontal. After this revelation, the surgical option was no longer considered. During treatment with intravenous gamma-globulins (age 10 years 8 months) there was a marked reduction in epileptic activity during sleep, but without any improvement in the cognitive situation. An increase in the frequency of the epileptic seizures was reported during this phase, primarily nocturnal. This could be treated with lamotrigine.

Patient 7: This girl (1990) was born prematurely. Breathing problems were present postpartum and she was given a drain in connection with hydrocephalus. CT-scan examination showed hypodensity right fronto-parietal, probably the result of a haemorrhage. The onset of epilepsy occurred at the age of 4½ years, with convulsions in the left hand without loss of awareness. Later these convulsions spread over the whole left body half. She was treated with carbamazepine, later in combination with clobazam. The EEG showed increasing local epileptic activity right temporal. The attacks continued however and were now accompanied by lowered awareness. Other anti-epileptic drugs (oxcarbazepine, vigabatrin, valproate) also had no effect. At the age of 5 years 9 months the attacks were reacting favourably to oxcarbazepine and clobazam. It was then that scholastic and behavioural problems were reported. An EEG during sleep showed continuous epileptic activity, with the exception of the REM phase. The SW index was more than 85%. During the daytime there was diffuse spike wave activity and also local epileptic discharges right frontal. CSWS was diagnosed. Treatment with gamma globulins and later with prednisone had no effect. The last EEG during sleep showed continuous epileptic activity in the form of diffuse, but predominantly right, spike wave activity during 65% of the sleep period. Her cognitive level dropped from a total IQ of 72 at 5 years 9 months (with significantly weaker non-verbal scores) to an IQ of 43. From a cognitive point of view the right hemisphere continued to present the most problems.

Patient 8: This girl was born in 1989 by forceps extraction, in connection with foetal distress. At the age of 3½ years she was given speech therapy because of a language development deficit. During her 5th year her development came to a relatively sudden halt; she withdrew into herself and barely communicated anymore. Psychological examination revealed few non-verbal problems, but a language development test turned out to be impossible. Audiological examination revealed nothing exceptional. The MRI showed no abnormalities. Diurnal EEG examination showed a great many diffuse epileptic discharges. The EEG during sleep showed continuous diffuse bilateral spike wave activity, with the exception of the REM phase. This phase showed left-fronto-temporal local high-voltage slow activity. There were no epileptic seizures. On the basis of the clinical symptoms and the EEG, the diagnosis Landau-Kleffner Syndrome was made and the patient was put on valproate. This had no result. Intermittent corticosteroid treatment was then started. In the first week she was given 1 mg dexamethason, in the second week 0.5 mg. After this the dexamethason was stopped. After five days of treatment a marked improvement in the clinical picture occurred. A regression became apparent after nine weeks, a second regression after nine weeks, a third regression after sixteen weeks, a fourth after twelve weeks, and a last after eleven weeks. Each regression reacted well to dexamethason. After the final course of dexamethason the language problems stayed away definitively. An EEG at 9½ years was normal. Psychological examination at 9 years showed that the language deficit had been substantially but not completely eliminated: language comprehension remained somewhat retarded, auditive memory also remained weak. After a few years of special education for hearing impaired children with language deficit this patient was able to resume regular primary education.

Patient 9: This patient was born in 1988 in breech presentation. She developed normally until her first year. Hearing problems were then suspected, but had not been confirmed by an E.N.T. specialist. At 18 months a relatively retarded speech-language development was suspected. She had her first epileptic attack at the age of 4 years, with convulsions in the right hand and impaired consciousness. The EEG showed an epileptic focus left temporal with spreading to the rear. No EEG during sleep was made at this time. Linguistic examination revealed a language development deficit

of more than a year, with regard to both expression and comprehension. Psychological examination determined an IQ level of 77, with hyperactivity and poor memory recall. In connection with the epilepsy she was put on carbamazepine. Six months later both diurnal and nocturnal EEGs showed bilateral occipital continuous epileptic activity. The combination of the clinical picture and EEG results suggested Landau-Kleffner Syndrome. At 5 years 2 months, with carbamazepine as medication, the EEG was unchanged. Language comprehension had increased by one year, language production remained stagnant at 3-3½ years. As she got older she progressed but only slowly. At 9 years 4 months the EEG was more or less normal with only sporadic sharp activity left central. Language production then scored at 5.1 years and language comprehension at 6.3-7.7 years.

Patient 10: This girl (1982) developed relatively normally during her first 4 years. During her 4th year she was examined for suspected deafness. Hearing tests were inconclusive. Her hearing problems continued despite a tonsillectomy, an adenotomy and the placing of tubes. Complex partial seizures with vomiting were reported from her 5th year. She also developed progressive word finding problems, articulation problems and concentration problems. Comprehensive examination by a paediatric neurologist followed at the age of 6 years 6 months. Comprehensive metabolic examination, CT-scan and SPECT did not reveal any abnormalities. The diurnal EEG showed epileptic activity right fronto-central, with spreading to the front and rear but also to the left. During sleep the epileptic activity increased considerably: continuous generalised diffuse spike wave activity during 50% of the sleep period, with the exception of the REM phase. During this phase there was only epileptic activity on the right. On the basis of the clinical symptoms (auditory agnosia, acquired aphasia) and the EEG results, Landau-Kleffner Syndrome was diagnosed. Treatment with carbamazepine resulted in a worsening of the clinical picture: linguistic communication became impossible; she only produced noises. Exploratory psychological examination determined a non-verbal level in accordance with her age. The EEG now showed continuous epileptic activity during more than 80% of the sleep period, with the exception of the REM phase. Carbamazepine was replaced by valproate, partly because of the continuing complex partial seizures. This resulted in the cessation of the seizures and a slow but steady

alleviation of the language problems. At the age of 9 years and 8 months the EEG during sleep still showed continuous epileptic activity during 50% of the sleep period. By the age of 11 years and 11 months the epileptic abnormalities had disappeared. During her 14th year psychological examination showed a good development of scholastic skills. Her non-verbal scores were then average (97), but there was still a language comprehension deficit.

Chapter 9

Status Epilepticus in Mentally Retarded Patients: Causes and Outcome in 170 patients

Submitted

Summary
Status epilepticus in patients with mental retardation has not often been subject of a separate study. We present the results of status epilepticus in 113 adults and 57 children with mental retardation. The most frequent type was tonic-clonic status epilepticus, both in adults and children. Most patients with tonic-clonic status epilepticus had previous epilepsy. In only two adult cases and in one child an acute symptomatic cause was present. Causes included systemic infections and low anti-epileptic drugs levels. The other cases were idiopathic. Outcome was comparable to cases without mental retardation but with previous epilepsy, and not related to duration of status epilepticus. Outcome in patients with one or more medical complications was poor; this was especially true for children. Particular types of status epilepticus, occurring especially in mental retardation, include tonic and atypical absence status epilepticus. Within the group of non-convulsive status epilepticus a considerable number of cases with complex partial status epilepticus were present.

9.1 Introduction

According to Shorvon (1994) the risk of status epilepticus (SE) in patients with epilepsy and mental retardation (MR) is high (Shorvon, 1994). Little information about prevalence and incidence of SE in patients with MR is available, however, some studies mentioned the prevalence; these figures are not very different from those in the general population (Forsgren et al, 1990; Phillips et al, 1996; Steffenburg et al, 1996; Hauser, 1990; Sillanpää et al, 1998). It is possible that many cases of SE in patients with MR are not documented. This is supposed to be the case especially for non-convulsive SE (NCSE), a diagnosis easily overlooked in patients with MR, with an annual incidence estimated to be 100-200 per 1.000.000 persons in the general population (Shorvon, 1994; Brodtkorp et al, 1993). Little is known about the causes of tonic-clonic SE (TCSE) in MR. Outcome of generalized convulsive SE (GCSE) in MR has not been subject of a separate study. Outcome of NCSE in MR is uncertain. Some studies failed to show an effect of NCSE on outcome in MR (Dravet et al, 1985; Beaumanoir et al, 1988), while others described cognitive deterioration after one or more periods of NCSE (Moe, 1971; Doose and Völzke, 1979; Hoffmann-Riem et al, 2000).

Therapy of GCSE in MR has not been the subject of separate research. In contrast, several authors discussed treatment of NCSE in MR, but the results were often disappointing (Shorvon, 1994; Brodtkorp et al, 1993; Beaumanoir et al, 1988; Brett, 1966).

We have performed a retrospective study of SE in MR to investigate whether specific features were present, which were different from SE in the population without MR. We were particularly interested in causes and outcome of TCSE in MR. In accordance with the definition of SE, as proposed at the symposium at Santa Monica, we included only cases with a minimum seizure duration of 30 minutes or an established succession of generalized convulsive seizures without regaining consciousness between the seizures (Delgado-Escueta et al, 1983). The classification of the various types of SE occurred according to seizure type (Gastaut, 1983). Causes of SE included acute symptomatic causes, a progressive neurological disorder and unknown. Many patients with MR will have previous epilepsy, caused by a remote symptomatic neurological problem; we considered the cause of SE in these patients unknown (and not remote symptomatic) when an acute symptomatic cause or a progressive neurological disorder was not found. Our cohort of patients in 12 hospitals and 2 epilepsy centres amounts to 576 adult cases and 112 children. Mental retardation was present in 113 adult patients and in 57 children. The level of MR could be estimated on the basis of file information.

9.2 Results

In the total group, 24.75% had MR, in the children group 53%. Patients with MR were more prevalent in the epilepsy centres and the small hospitals (table 1-a and 1-b). SE in MR showed a male preference in both adults and children. Generalized convulsive SE (GCSE) was the most frequent type of SE: 81% in adults and 66,7% in children (table 2). Mental retardation was moderate to severe in most patients. Only two adults (27 and 28 years of age) and one child (11 years) with GCSE never had seizures before; the cause of SE in both adults remained unknown, encephalitis was the cause in the child. In eight adult patients with MR the diagnosis SE appeared wrong: four with serial seizures, three with only one seizure of usual duration, and

one patient was known with previous epilepsy, but did not have a seizure when he was admitted. The diagnosis SE was correct in all children.

Table 1-a: Hospital type and Status Epilepticus (SE) in adult patients in the Netherlands

Hospital type	University (6)	Large (2)	Small (4)	Epilepsy centre (2)
Admissions	300	113	98	65
Number of SE	247	67	90	54
Number of SE/year	5.4	4.5	4.7	3
Previous epilepsy (%)	66	52	69	100
MR (%)	18	7	28	39

Table 1-b: Hospital type and status epilepticus in children

Hospital type	University (6)	Large (2)	Small (4)	Epilepsy centre (2)
Number of SE	77	3	6	26
Previous Epilepsy (%)	53	100	100	100
MR (%)	37	100	33	88

Table 2: Age and type of SE in patients with MR*

Type of SE	Age 1-5	Age 5-15	Age 15-30	Age 30-50	Age >50
GCSE	18	20	42	37	13
EPC	1	1	1	4	0
NCSE	1	16	7	1	0
No SE	0	0	4	3	1
Total	20	37	54	45	14

* Absolute numbers. GCSE= Generalized Convulsive SE; EPC= Epilepsia Partialis Continua; NCSE= Non-Convulsive SE; No SE= wrong diagnosis of SE.

Generalized Convulsive Status Epilepticus (GCSE)

In 91 of 92 adult patients (15-71 yrs) TCSE was present; one patient had myoclonic SE (MSE) of unknown cause. Recurrent TCSE occurred in 5

patients. In 36 children TCSE was present; one child showed tonic SE (TSE) of unknown cause and another child with tuberous sclerosis MSE, cause also unknown. The causes of GCSE are presented in table 3. The cause was unknown in most adult cases; in two adult patients a new neurological problem, a cerebral infarction (CVA), caused GCSE. These two patients were known with previous epilepsy; one patient had a good outcome, the other showed persistent hemiparesis after GCSE. In children systemic infections with fever appeared the main cause of GCSE; in about 43% the cause remained unknown. In one child, in who encephalitis was the cause of GCSE, the outcome was good. Low levels of AED as a cause of GCSE were more frequently found in adults than in children.

GCSE was continuous in 59 adults (64%) and in 35 children (92%). Outcome in continuous GCSE was good in 81.4% of the adults and in 97% of successive SE. Duration of GCSE varied from 30min to more than two days. Duration was less than 4 hours in 74% of the children and in 66% of the adults. A relation between outcome and duration could not be established.

Outcome is mentioned in table 4. Morbidity in eight adults, seven with continuous GCSE, was caused by the underlying aetiology in two and by SE itself in four patients. Morbidity in eight adults consisted of hemiparesis (three), impaired consciousness (one), renal disturbance (one), cognitive deterioration (one), persisting myoclonic jerks (one). One patient was transferred in SE to another hospital. Morbidity caused by SE itself in adults consisted of hemiparesis (two), renal disturbance (one) and cognitive deterioration (one). SE itself caused mortality in two of four adults with continuous GCSE, whereas the underlying aetiology was responsible in one patient. SE itself caused morbidity in one of two children with continuous GCSE. In children morbidity consisted of aphasia with visual disturbance in one (because of SE itself) and persistent myoclonic jerks in another patient (of unknown cause). Mortality in three children (all with continuous GCSE) was caused in all three by SE itself.

Adult patients with previous epilepsy but without MR had comparable outcome to patients with MR; in children without MR outcome appeared worse than those with MR, but the number (13) of this group is too low to allow firm conclusions (Table 4).

Medical complications during GCSE occurred in 33,7% of adult patients and in 30% of the children. Medical complications consisted of aspiration,

respiratory insufficiency, acidosis, hyperthermia and liver failure. Outcome in cases without medical complications was better than in patients with one or more medical complications, especially in children (Table 5).

Therapy was adequate in adults in 75 patients, with good outcome in 89,3%. Therapy was inadequate in 15 adult patients, with good outcome in 80%. In two cases the quality of therapy was hard to define. In children therapy was adequate in 25, with good outcome in 80%. Therapy was inadequate in 13, with good outcome in 92,4%.

Inadequate therapy consisted of diazepam i.m., phenytoin i.m., no loading-dose of phenytoin, no therapy or insufficient dose.

In both adults and children benzodiazepines (BDZ) and/or phenytoin (PHT) were the most frequent used anti-epileptic drugs (AED) to terminate GCSE: in 80 adults and 30 children. Other AED in adults were thiopental (four), chlormethiazole (one), etomidate (one), chloralhydrate (one); in one case all drugs failed, in four no therapy was instituted. In children other drugs consisted of phenobarbital (one), thiopental (two), valproate (one); in four children all drugs failed.

Table 3: Causes of GCSE in adult patients and children with MR*

Causes of GCSE	Adults (92)	Children (38)
Unknown	64	16
Low levels of AED	22	3
Systemic infections	4	12
CVA	2	0
Progressive neurological disease	0	5
Encephalitis	0	1
Stress	0	1

* Absolute numbers

Table 4: Outcome (%) in GCSE in adult patients and children*

	Outcome Good	Morbidity	Mortality
GCSE adults total group (346)	76	13	11
GCSE adults previous epilepsy, no MR (144)	84,7	8,3	6,9
GCSE adults and MR (92)	87	8,7	4,3
GCSE total group children (82)	75	12,5	12,5
GCSE children and MR (38)	86,9	5,2	7,9
GCSE children previous epilepsy, no MR (13)	77	7,7	15,3

* Absolute numbers between brackets

Table 5: Medical complications in relation to outcome (%) in GCSE*

Medical complications	Outcome Good	Morbidity	Mortality
Adults (92)			
No complications (61)	91,8	4,9	3,3
1 or more (31)	77,4	16,1	6,5
Children (38)			
No complications (27)	96,3	3,7	0,0
1 or more (11)	63,6	9,1	27,3

* Absolute numbers between brackets

Epilepsia Partialis Continua (EPC)

EPC was present in five adults and two children. Duration varied between two hours and two years. Outcome in the adults was good in three; one patient with a brain tumour has hemiparesis; one patient continued to show EPC. Both children died.

Non-Convulsive Status Epilepticus (NCSE)

In the eight adults with NCSE, CPSE was present in seven and atypical ASE in one. All were known with previous epilepsy. NCSE in the 17 children consisted of CPSE in eight, atypical ASE in seven; 2 children with pre-existent MR developed continuous spikes and waves during sleep (CSWS). All children with NCSE were known with previous epilepsy of unknown cause, except for one child with Andermann syndrome, who showed atypical ASE. The adult

patient and the children with atypical ASE showed continuous slow spike-wave activity with the highest amplitudes in both fronto-temporal regions on the EEG. In four adults and six children with CPSE the diagnosis was made on clinical grounds (partial seizures in patients known with previous partial epilepsy) because no EEG investigation has been performed during SE. In three adults and two children with CPSE, the EEG investigation confirmed SE. In both children with CSWS, repeated overnight EEGs showed continuous diffuse spike-wave activity in more than 85% of the total sleep duration, with the exception of the REM-phase.

The cause of NCSE in children was unknown in 11; in six cases low AED levels appeared responsible. In adults NCSE was caused by systemic infections in two, low AED levels in four, a progressive neurological disease in one, whereas the cause remained unknown in another case.

Duration of CPSE in adults varied from less than two hours in two patients to more than two weeks in one; the duration in the case with atypical ASE was 2 days. Duration of atypical ASE in children was more than one day in six cases; five children with CPSE had duration of less than four hours and in two cases of two days.

Therapy was adequate in 60% of both adults and children with NCSE. NCSE in adults was terminated with BDZ in six, with thiopental in one and with PHT in another. No therapy given in two children, carbamazepine in one, chloralhydrate in one, PHT in one, whereas various drugs were without effect in another child, and BDZ in the remainder. Outcome was good in all cases, except in two children with CSWS who showed persistent cognitive decline.

9.3 Discussion

Little information can be found in the literature about the incidence, causes and outcome of SE in patients with MR. These patients are probably included in the total group of patients with SE (DeLorenzo et al, 1996; Hesdorffer et al, 1998; Coeytaux et al, 2000; Knake et al, 2001), but it is not correct to extrapolate the results in the total group to patients with MR. There are several arguments to state that SE in MR may present special characteristics with respect to clinical presentation, causes and outcome: the incompleteness of

cerebral development, the presence of specific aetiology, the fact that some MR-syndromes often show particular types of NCSE (Angelmann syndrome; Lennox-Gastaut syndrome) and that some types of SE (atypical ASE, TSE) occur almost exclusively in patients with MR. Another problem of SE in MR is that not all cases will be admitted to a hospital, and that documentation is incomplete. This is especially the case for NCSE in MR (Shorvon, 1994). A great part of NCSE is probably not recognized. It is also possible that not all patients institutionalised in an asylum with a TCSE will be admitted to a hospital, when local out-of-hospital treatment proved successful. Cases with TCSE who have been admitted to a hospital are resistant to AED of first choice, show medical complications or have been treated inadequately. The patients in our study represent the more resistant and/or complicated cases of SE in MR.

Our study was part of a large retrospective study of SE in the Netherlands. From a total group of 576 adults and 112 children with various types of SE we discussed the results in 113 adults and 57 children with MR and SE. GCSE was the most frequent type of SE in both adults (81,4%) and children (66,7%) with MR. NCSE was represented more in children (29,8%) than in adults (7,1%). EPC and NCSE were not found in the elderly group. The diagnosis of presumed GCSE appeared wrong in eight adults. The group of MR patients with GCSE was characterized by the high percentage of previous epilepsy (98,2% in both adults and children). In only two adults and one child an acute symptomatic cause was present. Causes of GCSE in adults included low levels of AED (24%) and systemic infections (4,3%), but in the majority the cause of SE remained unknown (69,5%).

In mentally normal patients with previous epilepsy, acute symptomatic causes (8,3%) and systemic infections were more prevalent and the unknown cases (32%) less. The number of cases with low levels of AED (30%) was comparable to patients with MR, although in the group without MR non-compliance was more often mentioned in this respect. In a considerable number of patients without MR alcohol (9,7%) was reported as cause of SE, a feature not present in MR (Scholtes et al, 1994). With respect to the causes of GCSE in children with previous epilepsy, with or without MR, no differences were found in the rates of systemic infections, low levels of AED or the number of unknown cases. A progressive neurological disorder as a cause was only present in MR (Scholtes et al, 1996). Outcome in GCSE did not differ from cases with previous epilepsy without MR.

Several factors that may contribute to outcome in GCSE were investigated. The most important factor with regard to outcome is the underlying cause (Lowenstein and Alldredge, 1993; Barry and Hauser, 1993). Our group of patients were in most cases known with previous epilepsy and showed a low number of acute symptomatic causes. Other factors with respect to outcome are duration (Aminoff and Simon, 1980; Barois et al, 1985) or treatment of SE (Lowenstein and Alldredge, 1993; Delgado-Escueta and Enrile-Bascal, 1983). Our study could not find a relation between duration of GCSE or the quality of therapy and outcome. Perhaps the low level of intelligence makes subtle cognitive morbidity unnoticed. The presence of one or more medical complications was related to poor outcome, especially in children.

There was a relation between outcome and SE itself in six adults and four children. Morbidity because of SE itself was present in 4,3% of the adults with MR and in 2,6% of the children; mortality because of SE itself was 2,1% in adults and 7,9% in children. Compared to the patients with SE without MR from our large SE-study, no differences were found between children with or without MR with respect to the contribution of SE itself to outcome. In adults more patients without MR died because of SE itself (13,2%) than adults with MR (2,1%); the rates of morbidity because of SE itself were comparable in adults.

Most cases with GCSE concerned TCSE. Specific types of SE in MR were limited to atypical ASE (1 adult and 7 children) and TSE (1 child). The number of cases with CPSE in both adults and children was striking. One may criticize our assumption that cases with previous partial epilepsy and NCSE were categorized as probable CPSE, despite the absence of EEG investigation during SE. It seems, however, acceptable to make the diagnosis of (probable) CPSE, based on the clinical presentation with focal neurological signs in a patient with documented previous partial epilepsy (and not symptomatic generalized epilepsy), together with the results of anti-epileptic drug treatment. These features make another diagnosis of atypical ASE (especially in patients with symptomatic generalized epilepsy), post-ictal confusion or pseudo-SE most unlikely.

This study has shown that outcome of SE in MR patients admitted to a hospital is comparable to patients with previous epilepsy but without MR. The assumption that especially the more resistant and/or complicated cases with SE in MR are admitted to a hospital, suggests that outcome of SE in MR is not poorer but rather more favourable than in non-retarded people.

The present results call for a prospective population based study of SE in MR to overcome the drawback of this retrospective study. Case-ascertainment in patients with MR is difficult. Therefore, cooperation with caregivers working in hospitals or asylums for patients with MR, with general practitioners (who take care of patients with MR who live at home) and with paediatricians is mandatory in this respect.

Chapter 10

Admissions to the Intensive Care Unit because of Generalized Convulsive Status Epilepticus

Summary
We studied 110 adults and 35 children admitted to the Intensive Care Unit because of Generalized Convulsive Status Epilepticus (GCSE). Causes of GCSE in adult patients with previous epilepsy were non-compliance and systemic infections, in children systemic infections. Acute symptomatic causes in adult patients without previous epilepsy were stroke, intoxication, metabolic disturbances and brain tumours; in children the main causes were bacterial meningitis and viral encephalitis. In comparison to cases with GCSE not admitted to the ICU outcome was worse. Especially cause and the number of medical complications determined outcome. Especially in children more severe cases with GCSE occurred, which caused a significantly worse outcome in children with previous epilepsy.

10.1 Introduction

Admission to the Intensive Care Unit (ICU) because of status epilepticus (SE) may be necessary especially when medical complications, such as respiratory insufficiency, are present, or when anaesthesia is mandatory to control SE. Few studies describe characteristics of adult patients and children with SE admitted to the ICU (Goulon et al, 1985; Nouailhat et al, 1985; Barois et al, 1985; Lacroix et al, 1994; Eriksson and Koivikko, 1997; Holtkamp et al, 2005). Other studies describe treatment of SE in the ICU in small cohorts of patients with anti-epileptic drugs such as midazolam, thiopental or propofol (Osorio and Reed, 1980; Orlowski et al, 1984; Lowenstein et al, 1988; Ness, 1990; Kumar and Bleck, 1992;Yaffe and Lowenstein, 1993; Parent and Lowenstein, 1994; Stecker et al, 1998; Claassen et al, 2001; Prasad et al, 2001; Claassen et al, 2002).

Most adult patients admitted to the ICU because of SE are not known with previous epilepsy, show a large percentage of acute neurological insults and a high morbidity and mortality rate (Goulon et al, 1985; Nouailhat et al, 1985; Yaffe and Lowenstein, 1993). Outcome is especially determined by the underlying cause; a relation with duration of SE was not always present (Goulon et al, 1985; Nouailhat et al, 1985). A drawback of these studies was the inclusion of different types of SE, which make it difficult to draw conclusions about outcome (Goulon et al, 1985; Barois et al, 1985).

In children generalized convulsive status epileptics (GCSE) occurs especially in the younger age group without previous epilepsy (Aicardi and Chevrie, 1970; Yager, 1988; Philips and Shanahan, 1989; Lacroix et al, 1994; Eriksson and Koivikko, 1997) and outcome is especially determined by the underlying cause, age, but also by duration of SE (Aicardi and Chevrie, 1970; Barois et al, 1985; Dunn, 1988; Yager, 1988; Maytal et al, 1989; Philips and Shanahan, 1989; Lacroix et al, 1994; Eriksson and Koivikko, 1997). Acute neurological causes are more frequent in the younger age groups (Philips and Shanahan, 1989; Lacroix et al, 1994; Eriksson and Koivikko, 1997).

GCSE may be the reason for admission to the ICU, but SE may also occur during the stay at the ICU because of another medical problem (Goulon et al, 1985; Nouailhat et al, 1985). Apart from clinical evident cases of convulsive SE, non-convulsive SE may be diagnosed in cases with impaired consciousness of unknown cause, without clinical evident seizure activity (Young et al, 1996; Lowenstein and Alldredge, 1992; Litt et al, 1998; Towne et al, 2000; Varelas et al, 2003).

This retrospective study was part of our investigation about therapy and outcome of SE in the Netherlands (chapter 2). We studied 110 adults and 35 children admitted because of GCSE to the ICU. We investigated causes and outcome of patients with GCSE admitted to the ICU and compared the results to patients not admitted to the ICU. Only patients with minimum seizure duration of 30 minutes or an established succession of generalized convulsive seizures without regaining consciousness between the seizures were included. Those who developed SE during their stay at the ICU and cases with non-convulsive SE or elementary partial SE were not included. The effects of the administered anti-epileptic drugs could be adequately studied in 41 adult patients and 35 children. The documentation of the results of the various drugs used before and during their stay at the ICU to treat SE was adequate in these patients. In the other adult patients especially the drugs used to terminate SE had been adequately mentioned, but those used earlier with less details.

10.2 Results

Age, gender and number of patients with previous epilepsy are presented in table 1.

Table 1. Age, gender and number of previous epilepsy of patients admitted to the ICU*

	Male	Female	Previous Epilepsy	Age 15-30	Age 30-50	Age >50
Adult patients	61	49	66 (60,0%)	36	39	35
	Male	Female	Previous epilepsy	Age <1	Age 1-5	Age 5-15
Children	20	15	14 (40,0%)	6	20	9

* Absolute numbers.

The number of adult patients *with previous epilepsy* was higher (60%) than in the group of children (40%). Precipitating factors, responsible for GCSE in adult patients with previous epilepsy were non-compliance and systemic infections with fever (table 2). The patients with a progressive neurological disease were suspected to have a mitochondrial encephalopathy. Other causes included a patient with carbamazepine intoxication (level 32 mg/l), who died because of GCSE.

In adult patients *without previous epilepsy* CVA was a prominent cause, especially in the older age group. Toxic causes included ethyleneglycol-intoxication with several medical complications and good outcome, amipaque (after caudography) and cyclosporine; metabolic causes included hyperglycaemia (level >36 mmol/l), hypokaliaemia (2,0 mmol/l) and hypocalciaemia (1,38 mmol/l). Brain surgery had been performed in a patient with a meningeoma and in a patient with a craniopharyngeoma. One patient with a brain tumour (malignant meningeoma) developed GCSE during radiotherapy.

In children systemic infection was the main precipitating factor in cases *with previous epilepsy* (table 2). In children *without previous epilepsy* bacterial meningitis and viral encephalitis were the most important causes

of SE. Three of them had herpes simplex encephalitis, all with good outcome. Two children with laryngo-bronchitis had a cardiac arrest and had to be resuscitated; both died. Two children developed severe hypoxia (one shortly after a cardiac operation, one because of a severe pulmonary infection); both died. The toxic causes consisted of one case of CO-intoxication (this patient died) and a patient who had been treated with cytostatica because of a medulloblastoma. This last patient showed cognitive disturbances after GCCE. The metabolic problem included a case with severe hypernatraemia (sodium level 160 mmol/l), who developed GCSE during rehydration.

Table 2: Causes and precipitating factors of GC-SE*

	Adults	Age <1	Age 1-5	Age 5-15
Previous epilepsy	66	0	8	6
Non compliance/lowering AED	16	0	2	1
Systemic infection	11	0	5	2
Progressive degenerative disease	4	0	0	0
Alcohol	5	0	0	0
Head trauma	2	0	0	0
Other	5	0	0	1
Unknown	23	0	1	2
No previous epilepsy	44	6	12	3
CVA	15	0	0	0
Toxic	5	0	1	1
Metabolic	4	1	0	0
Cardiac arrest	3	0	0	0
Brain surgery	2	0	0	0
Head trauma	2	0	2	0
Meningitis/encephalitis	3	2	4	2
Brain tumor	4	0	0	0
Multiple sclerosis	2	0	0	0
Unknown	4	1	0	0
Hypoxia/resuscitation	0	2	2	0
Systemic infection	0	0	3	0

* Absolute numbers.

Table 3: Outcome in GCSE*

Outcome	Good	Morbidity	Mortality
Adults			
Total (110)	56,3	20,9	22,7
Previous epilepsy (66)	66,7	15,1	18,2
No previous epilepsy (44)	40,9	29,5	29,5
Children			
Total (35)	42,8	25,7	31,4
Previous epilepsy (14)	42,9	21,4	35,7
No previous epilepsy (21)	42,8	28,6	28,6
Non-ICU adults: Total (236)	82,7	9,6	7,6
Previous epilepsy (169)	92,3	5,9	1,8
No previous epilepsy (67)	58,2	19,4	22,4
Non-ICU children: Total (47)	95,7	4,3	0
Previous epilepsy (37)	100	0	0
No previous epilepsy (10)	80	20	0

* Non-ICU refers to patients (GCSE) not admitted to the ICU.

Outcome appeared to grow worse with increased duration in children, most evident after 2 hours. This was evident when SE itself had determined outcome. When outcome had been determined by the underlying cause, a relation with duration could not be established in both children and adults. The relation between outcome and duration in adults was less evident for total morbidity and mortality. When restricted to cases where SE itself had determined outcome, morbidity increased especially after 2 hours and mortality after 8 hours. In adult cases with morbidity and mortality determined by SE itself, duration of GCSE was in most cases longer than 8 hrs (66,7 % of the cases with morbidity, 60 % of mortality). In children poor outcome determined by SE itself occurred in 75% of the cases with duration longer than 8 hours.

In children and adult patients outcome was worse when more than one medical complication was present (table 3).

Treatment of patients with GCSE in the ICU consists not only of adequate administration of anti-epileptic drugs but also of monitoring of ventilation,

blood pressure and heart rate and subsequent treatment of present abnormalities. The same goes for other possible medical complications such as acidosis, hyperthermia, and renal failure in cases of rhabdomyolysis. Based on information from the literature epidural intra-cranial pressure (ICP) monitoring was started (5 adult patients and 10 children) in complicated cases treated in a university medical centre. All patients with ICP-monitoring, except one, showed increased ICP with values varying from 40-100mmHg (normal less than 15). In several cases cerebral perfusion pressure (CPP) was at times almost zero, or at least too low for sufficient brain circulation. In one adult and in one child we found a relation between the start of a seizure (EEG monitoring) and the subsequent rise of ICP. Outcome in patients who had ICP-monitoring was poor. Only one adult patient and one child had a good outcome, whereas three adults and 7 children died.

Outcome in cases who needed mechanical ventilation was poor. Mortality in children was 46,4% and in adults 41,9%. No patients died in cases that did not need mechanical ventilation.

Table 4: Relation between outcome and medical complications*

Outcome	Good	Morbidity		Mortality	
Complications children		Total	SE	Total	SE
No (17)	64,7	29,4	5,9	5,9	0
1 (2)	100	0	0	0	0
> 1 (16)	12,5	25,0	6,25	62,5	31,25
Complications adults					
No (33)	63,6	27,3	0	9,1	0
1 (31)	74,2	19,3	3,2	6,4	3,2
> 1 (46)	39,1	17,4	8,7	43,5	28,3

* Absolute numbers between brackets

The effects of the administered anti-epileptic drugs were studied in 41 adult patients and 35 children (table 4). In cases with good outcome (16 adults, 15 children) therapy was insufficient in 27%, in cases with sequel (12 adults, 9 children) in 31,5% and in patients who died (13 adults, 11 children) in 54%. No differences were present between adults and children. Therapy was good in the two cases with sequel because of SE and in 5 of the 7 cases that died

because of SE. The quality of therapy did not influence outcome in cases with morbidity or mortality caused by SE itself.

The number of patients who were successfully treated with BDZ (especially diazepam and clonazepam, in some cases clorazepate) was low. A few patients (3 children) showed a positive effect during clorazepate infusion, whereas thiopental was not successful in these cases. The number of successfully treated cases with PHT was also low, but proper loading was done in only a few patients. Phenobarbital (PB) in children was ineffective in all cases, possibly because of a low dose. Thiopental was used only in cases when BDZ, PHT or PB was ineffective. Chlormethiazole had been tried in 3 adult patients (2 successful) and 2 children (1 effective) after the use of thiopental. Etomidate was used only after failure of thiopental. The miscellaneous drugs consisted of valproate, carbamazepine and acetozalomide. In one adult case GCSE subsided without further intervention; this patient showed no effect of BDZ and PHT. In 7 adult patients and 8 children all therapy was without any evident effect; they died.

Drugs used in the other adult patients to terminate GCSE consisted of: BDZ (24%), PHT (20,3%), PHT+BDZ (8,5%), thiopental (22%), etomidate (10,2%) and chlormethiazole (1,7%). In 13,5% none of the administered drugs were successful.

Table 5: Anti-epileptic drug therapy in GCSE*

		Adults (41)		Children (35)	
		Used	Successful	Used	Successful
Benzodiazepines	i.v.	44	17	33	12
Phenytoin	shot i.v.	23	1	22	2
	loading	6	0	1	0
	i.m.	1	0	0	0
	+ BDZ	4	4	0	0
Phenobarbitone	i.v.	2	0	20	0
	i.m.	2	0	2	0
Thiopental	shot i.v.	1	0	2	2
	infusion	11	7	16	10
Chlormethiazole infusion		5	4	2	1
Etomidate infusion		2	0	3	0
Chloralhydrate rectal		0	0	5	0
Miscellaneous		1	0	3	0

* Absolute numbers

Morbidity (20,9%) and mortality (22,7%) in the adult patient group, but also in children, 25.7% respectively 31,4%, were both especially determined by the underlying cause.

Morbidity and mortality in adult patients with previous epilepsy were lower than in patients without previous epilepsy, but worse than in patients with previous epilepsy not admitted to the ICU (table 5). Outcome was worse than in cases not admitted to the ICU; the difference in cases without previous epilepsy admitted versus not admitted to the ICU, was not as obvious as in children. This underlines the significance of the underlying cause with respect to outcome in adults. It was striking that outcome in the group of children with previous epilepsy was just as bad as those without previous epilepsy (table 5). Outcome in children not admitted to the ICU was far better, also for those without previous epilepsy. This may be explained by the fact that cases admitted to the ICU suffered from more severe GCSE. Morbidity in children of less than one year was 33%, and in children of 1-5 yrs 30%; mortality was 50 and 30% respectively. In older children (5-15 yrs) morbidity and mortality was 11% respectively 22%.

Morbidity because of SE per se in adult patients was 4,5%, in children 8,5%; for a group of 236 adult patients, not admitted to the ICU, 2.8% and for children 0%. Mortality because of SE per se in adult patients was 11,8% and in children 14,3%. In the non-ICU group this was only 3.6% for adults and 0% in children. These figures also make clear that cases admitted to the ICU suffer from a more severe GCSE.

10.3 Discussion

Admittance because of GCSE to the ICU was necessary because of failure of first line drugs (BDZ, PHT) or the occurrence of medical complications such as respiratory insufficiency. Outcome was especially determined by the underlying cause, both for adults and children. These results confirm earlier reports (Aicardi and Chevrie, 1970; Goulon et al, 1985; Nouailhat et al, 1985; Barois et al, 1985; Dunn, 1988; Yager, 1988; Philips and Shanahan, 1989; Maytal et al, 1989; Lacroix et al, 1994; Eriksson and Koivikko, 1997; Claassen et al, 2002). The less favourable outcome in the very young child or in the older age group and in patients without previous epilepsy is in accordance with this result. Causes and precipitating factors were not very different from other reports. Causes with a poor outcome were CVA and cardiac arrest in adult patients and in children resuscitation after laryngo-bronchitis and hypoxia and pneumococcal meningo-encephalitis. In children outcome was also related to the severity of SE, reflected by the results in children with previous epilepsy and by the results of therapy in cases where SE itself had determined outcome. We demonstrated a clear worse outcome in cases admitted to the ICU in comparison to those not admitted to the ICU. Apart from underlying cause, the seriousness of the cases with GCSE admitted to the ICU may be important with respect to this difference.

The relation between outcome and duration can best be discussed separately for cases where outcome is determined by the underlying cause and cases where SE itself has been the main determinant. When outcome is especially determined by the underlying cause, damage is present from the start of SE and the contribution of continuous seizures will be hard to establish.

Although a relation between duration and outcome has been suggested by several authors (Rowan and Scott, 1970; Aminoff and Simon, 1980; Barois et al, 1985; DeLorenzo et al, 1987; Eriksson and Koivikko, 1997), few described the distinction between underlying cause and SE itself in reporting the relation between outcome and duration of GCSE (Aminoff and Simon, 1980). Our study suggests a negative relation between duration of more than 2 hrs and outcome, especially in cases where SE itself was responsible for morbidity or mortality.

Others have already demonstrated that therapy delay (Rowan and Scott, 1970; Treiman et al, 1983; Lowenstein et al, 1988) contributes to a longer duration of SE, the same goes for inadequate therapy (Delgado-Escueta and Enrile-Bascal, 1983). Our observations about the role of medical complications and the quality of therapy confirm these findings. Our results also show that some patients with GCSE appear difficult to treat, despite adequate measures. These cases suffer from a severe type of GCSE, contributing to increased morbidity and mortality.

Treatment of SE should occur according to protocol, including a time schedule and an adequate choice of available AED (Scholtes et al, 1993). BDZ and PHT remain first line drugs, with adequate loading of PHT. In the ICU thiopental is an important drug when the first line drugs fail; our results have shown beneficial effects of thiopentone in difficult to treat cases with GCSE. Recent alternatives are midazolam or propofol infusion, but adequate trials comparing the results of various drugs in refractory SE are not yet available. In some cases even a forth or fifth drug appeared to be successful to terminate SE. EEG monitoring is very important, especially in cases that have been paralysed (mechanical ventilation), but also to adjust therapy. We have observed that in some cases the simultaneous recording of the EEG and ICP-monitoring a relation exists between seizures and the subsequent rise of ICP, which has been reported earlier (Tsementzis et al, 1979; Gabor et al, 1984). ICP monitoring may have important therapeutic consequences, because cerebral perfusion pressure may reach a critical threshold.

Outcome in patients admitted to the ICU because of GCSE is worse than in cases not admitted to the ICU. Apart from serious acute symptomatic causes, the severity of SE appeared also important with respect to outcome, stressing the importance of treatment according to protocol.

Chapter 11

Summary and Discussion

11.1 Introduction

Experiences with cases of status epilepticus (SE), refractory to first-line anti-epileptic drugs (AED), treated at the intensive care unit (ICU), initiated this study. Despite the presence of adequate medical literature about the pathophysiology and treatment of SE (Aminoff and Simon, 1980; Delgado-Escueta et al, 1983), patients with SE were treated without the presence of a protocol, even in the neuro-intensive care unit of a University hospital.

Most cases with SE are successfully treated with first-line AED, refractory cases occur less often. On the one hand this might explain the absence of such a treatment protocol, on the other hand it should have been the reason to initiate a protocol, especially in an University training hospital, where difficult to treat cases are often referred to. Another reason became evident when treatment according to protocol had been suggested (Scholtes and Dries, 1986), which caused opposition among several senior staff members; they preferred to stick to their own method. Based on our experiences the intention to promote therapy of SE according to protocol seemed logical, the criticism or opposition to introduction appeared a phenomenon that is often encountered during a process of transformation into a rational or evidence based protocol.

After the first attempt to initiate treatment of SE according to protocol an investigation was started to evaluate outcome and treatment of SE in the Netherlands. At that moment no data about this subject were available in the Netherlands. The foreign literature at that moment contained only retrospective, highly selective, studies with patients from university hospitals or specialized inpatient services, with considerable differences in age groups. Several drawbacks of these studies, apart from the retrospective nature, were apparent:

- The inclusion of different age groups.
- No distinction in patients with or without previous epilepsy.
- The inclusion of different types of SE.
- Variable duration of follow-up.
- Discussions about outcome without distinction between cases with or without previous epilepsy or between the different types of SE or without a relation with underlying cause and SE itself.

Recent prospective studies did not entirely overcome these problems, outcome was still reported irrespective the type of SE or the presence or absence of previous epilepsy. This was illustrated by the differences in outcome between the study from Germany (Knake et al, 2001) and the study from the USA (DeLorenzo et al, 1996). These differences appeared to be, at least partly, determined by differences in the numbers of patients with convulsive SE.

Information about the incidence of SE was not available at the start of this study and has been provided only recently by some prospective studies (DeLorenzo et al, 1996; Coeytaux et al, 2000; Knake et al, 2001).

We traced as many as possible admissions because of SE to a number of hospitals during the period 1980-1987. Included were only cases consistent to the current definition (Delgado-Escueta et al, 1983). The various types of SE were divided according to the current classification of SE (Gastaut, 1967).

In order to trace patients with SE in the several hospitals in the Netherlands we used dismissal diagnoses, coded according to the International Classification of Diseases of the World Health Organisation, the ICD-9, implemented by SIG and the hospitals in the Netherlands. This classification appeared to have limitations, because only three types of SE had been coded: petit-mal SE (code 345.2), grand-mal SE (code 345.3) and Epilepsia Partialis Continua (code 345.7). A separate code for e.g. complex partial (CPSE) or tonic SE (TSE) was not available. Still we did find a considerable number of cases with CPSE, although the dismissal code was different, such as petit mal SE or even grand-mal SE.

We encountered several other problems:

– A considerable number of cases with a wrong diagnosis of SE (No-SE).
– A wrong diagnosis of the type of SE, such as cases with elementary partial SE (EPSE) classified as CPSE, generalized convulsive SE (GCSE) or as petit mal SE.
– Duration of SE was not always recorded; in such cases duration could often be estimated with the help of information about transport and/or treatment duration. Only cases with known duration were included in the discussion about the relation between outcome and duration.
– Information about treatment initiated by the general practitioner or ambulance personnel was not always available.

– The number of seizures in successive SE was not always noted.
– Not all registered cases with SE could be traced.

The completeness of documentation of dismissal diagnoses in the hospitals we visited varied widely, which did not depend whether it was an academic hospital or not. In fact, the smaller hospitals appeared well organized in this respect and showed no or very few cases with No-SE. Some other features were striking, such as inconsistent loading of phenytoin or inconsistent EEG monitoring. This was especially the case in some of the academic hospitals. A treatment protocol was present in only one academic hospital and one epilepsy centre; it was not always followed, however. The other academic hospitals treated at random, possibly depending who was in charge as senior staff member.

Other investigators have mentioned the problem of a correct diagnosis of epileptic seizures or SE; SE was not recognized or the diagnosis appeared incorrect in a significant number of cases (Handforth et al, 1993; Garnett et al, 1994; Berger et al, 1999). They stressed the importance of the expertise of the neurologist or the 24-hour SE-Team in these sometimes-complex situations. In that way these problems we encountered, such as the incompleteness of files or the number of wrong diagnosis of SE (No-SE) appeared to be not very different from other studies in the literature.

Several studies have attempted to quantify the frequency of SE in various clinical populations. These surveys were until recently retrospective with inherent inaccuracies. Apart from the retrospective nature of most studies, there are several other potential problems one should consider:
– The diagnosis of SE in clinical practice is not always apparent.
– The diagnosis is not always considered, especially non-convulsive SE in mentally retarded patients or patients with confusion, mistaken for a psychiatric diagnosis.
– A number of cases will not reach a hospital; they are treated outside neurological services.
– SE in patients already admitted because of another medical problem will not always be documented as such.
– Duration of seizures will not always be recorded; short status episodes may be categorized as seizures, not as SE.

– In clinical practice therapy is not awaited for, but is instituted especially when an acute exacerbation is present in a patient known with previous epilepsy, or when serial seizures are present. An incorrect dismissal diagnosis of SE is not rare in these cases.

Recent prospective studies have mentioned the problem of under-ascertainment (DeLorenzo et al, 1995; Knake et al, 2001). Many cases of SE will not be brought to the attention of the adult and paediatric neurological staff and remain unidentified. Apart from these reasons we have mentioned the lack of adequate coding possibilities for types of SE. For all these reasons it is impossible to detect all cases of SE in a certain year.

Nevertheless, our study provided information about patients with SE, which is not present in the available, also recent, literature:

– Differences in outcome in cases with or without previous epilepsy.
– Causes of SE in patients with or without previous epilepsy.
– The relation between outcome and the presence of medical complications.
– The relation between outcome and duration of SE.
– The relation between outcome and treatment of SE.
– The relation between outcome and the underlying cause or SE itself.
– Information about SE in mentally retarded patients.
– Information about treatment of GCSE in the ICU.

In collaboration with Dr. G. Zielhuis of the Department of Epidemiology, we made the following assumption: a case with SE will be admitted to a hospital and documented by SIG; not all cases will be registered, such as cases with SE already hospitalised because of another medical problem or non-complicated cases, e.g. from asylums of mentally retarded patients or cases which have not been recognized as such. The study was thus focussed on more complicated cases, which had to be admitted to a hospital. Based on the number of documented cases by the SIG it was concluded that a number of 500 cases should be sufficient to answer the questions we posed at the start of this study.

Our cohort of patients from 12 hospitals and 2 epilepsy centres, spread all over the country, amounts to 576 adult patients and 112 children with various types of SE. This sample, representative for the situation in the Netherlands, has been used for further analysis of causes, therapy and outcome of SE in the Netherlands.

11.2 Results in adult patients (chapter 4-6)

In contrast to other reports, we studied outcome of SE in relation to the type of SE and the presence of previous epilepsy or not (table 1). Outcome per seizure type presents striking differences, especially when a distinction is made in cases with or without previous epilepsy.
The underlying cause is of major importance:

- Outcome of GCSE in cases with previous epilepsy is comparable to cases without previous epilepsy, when SE was caused by an acute symptomatic cause.
- Outcome in large and academic hospitals was less favourable than in smaller hospitals and epilepsy centres, reflected by the higher percentage of acute symptomatic cases and referral of more complicated cases.

Outcome in cases *without SE (No-SE)* appeared comparable to cases with previous epilepsy in the total group of SE and to cases with previous epilepsy from the group with GCSE (table 1).

By definition SE does not contribute to outcome in cases with No-SE. This group is especially composed of patients with some sort of epileptic problem (single seizure, serial seizures or just known with epilepsy). Morbidity and mortality in cases with No-SE was in all cases related to a specific cause: CVA (3), aspiration pneumonia, cerebral tumour (2), hypotension, Alzheimer disease, encephalitis, head trauma, progressive neurological disease of unknown origin and pseudo-tumour cerebri. If we compare the No-SE group with the total SE and the GCSE group one might conclude that the presence of SE is related to a worse outcome (table 1). This may be related to more severe cases of acute symptomatic cases in the SE group or to a negative contribution of SE itself or both.

TCSE is the most frequent occurring type of SE. Recent prospective studies suggest an incidence of TCSE of 5-30 per 100.000. Based on these numbers one may expect at leat 1000 patiënts with TCSE every year in the Netherlands.

Causes and precipitating factors of *TCSE* in adults were in accordance with the literature.

Apart from underlying cause we could demonstrate that outcome is worse when duration of SE was longer, when medical complications were present and when therapy was inadequate, especially in cases where SE itself was important to outcome. Some medical complications appeared more deleterious than others, especially respiratory insufficiency. We have shown that also in cases without medical complications patients may die because of SE, although this is not frequent (1-2%). We have investigated cases whose death or morbidity might have been preventable, such as cases with obvious inadequate therapy (waiting too long before initiating therapy; no ventilation and death because of respiratory insufficiency; continuous electrical SE without adjustment of therapy; insufficient anticipation of the potential lethal medical complications). On the other hand we came across cases with optimal treatment that nevertheless died because of SE.

Considering the recent prospective epidemiological studies one can estimate the total annual number of cases of SE in the Netherlands, but also the number of cases with TCSE in adults (Knake et al, 2001). We calculated an annual number of 636 adult cases with TCSE; our study suggests an annual morbidity and mortality because of SE in cases with inadequate therapy (chapter 4) in 10 respectively 24 cases, which may be prevented with the help of therapy according to protocol.

It is well known that the diagnosis of *NCSE* in clinical practise may be difficult and often even not considered. In a recent prospective study, with 24 hour EEG-monitoring possibilities, an incidence of 4.4 per 100.000 was reported (Coeytaux et al, 2000); other studies mentioned lower figures (0.65-1.2 per 100.000), but acknowledged significant case under-ascertainment (Tomson et al, 1992; DeLorenzo et al, 1996). Based on the figures from Switzerland one may expect about 700 cases with CPSE and 96 with ASE every year in the Netherlands.

Our retrospective study reported the results in 65 cases with NCSE, 40 with CPSE and 25 with ASE. The nature of this study and the fact that it concerned only cases admitted to hospitals, suggest a high number of more cases with NCSE, not admitted and/or not recognized as such, especially present in particular groups of patients (elderly or mentally retarded). Our group of patients with NCSE is one of the largest published until now.

We confirmed the good prognosis of ASE in all cases, despite inadequate therapy in some. Causes or precipitating factors of ASE were comparable to those mentioned in the literature.

Outcome in CPSE was especially determined by the underlying cause; the difference in outcome in cases with and without previous epilepsy was striking (table 1). All patients with previous epilepsy, except one had good outcome. This elderly patient died because of aspiration pneumonia acquired during CPSE. SE itself caused morbidity (memory deficit and word findings problems) in one patient without previous epilepsy; morbidity in the other 5 cases was determined with certainty by the underlying cause in 3 patients. Death in one case without previous epilepsy was also determined by its cause. To mention only total morbidity (15%) and mortality (5%) in CPSE, irrespective the presence of previous epilepsy or not, would have had less significance. A relation between outcome and duration could not be established. Quality of therapy was more often inadequate in cases with morbidity; in three patients this might have contributed to a worse outcome. During our investigation it was striking that therapy of NCSE was variable or even clearly inadequate. In cases with longstanding CPSE morbidity because of SE itself should be considered. Modern neuro-imaging techniques may provide more information and may contribute to the discussion about treatment of CPSE.

Table 1: Outcome of status epilepticus (SE) for the total adult group and per type of SE*

Outcome in adult patients	Good	Morbidity		Mortality	
		Total	SE	Total	SE
No-SE (118)	86.4	5.1	–	8.5	–
Previous epilepsy (69)	91.3	1.4		7.2	
No previous epilepsy (41)	78.0	12.2		9.8	
SE total (458)	76.0	14.7	4.8	9.5	5.1
Previous epilepsy (314)	87.0	6.4	3.8	6.4	3.5
No previous epilepsy (144)	57.0	19.8	2.1	22.6	8.5
GCSE (346)	76.0	13.0	3.5	11.0	6.1
Previous epilepsy (236)	85.5	8.5	3.8	6.0	4.3
No previous epilepsy (110)	55.5	22.7	2.7	21.8	9.9
GCSE (346)					
MR (92)	87.0	8.7	4.3	4.3	2.2
No-MR (254)	72.0	14.6	3.1	13.4	7.5
No-MR previous epilepsy (144)	84.7	8.3	3.5	6.9	5.6
No-MR no previous epilepsy (110)	55.9	22.5	2.7	21.6	9.9
GCSE					
Admitted at ICU (110)	56.3	20.9	4.5	22.7	11.8
Previous epilepsy (66)	66.7	15.1	7.5	18.2	16.6
No Previous epilepsy (44)	40.9	29.5	0	29.5	4.5
Non-ICU (246)	82.7	9.6	2.8	7.6	3.6
CPSE (40)	80.0	15.0	2.5	5.0	2.5
Previous epilepsy (28)	96.4	0	0	3.5	3.5
No previous epilepsy (12)	41.6	50.0	8.3	8.3	0
ASE (25)	100	0	0	0	0
SPSE (47)	70.2	21.3	2.1	8.5	0
Previous epilepsy (27)	85.2	14.8	3.7	0	0
No previous epilepsy (20)	50.0	30.0	0	20	0

* No-SE: wrong diagnosis of SE. GCSE: generalized convulsive SE; MR: mental retardation; ICU: intensive care unit; non-ICU: not admitted at the ICU; CPSE: complex partial SE; ASE: absence SE; SPSE: simple partial SE.

The incidence of *SPSE* has been reported recently in several prospective studies; based on these studies, one may expect an annual number of about 480 cases in the Netherlands. Most cases will be somatomotor, how many cases will correspond to EPC is unknown. Other types of SPSE are less likely to be recognized and reported.

We studied 47 patients with SPSE; somatomotor type was present in 46, and 20 of these corresponded to EPC. It was striking that also in cases with previous epilepsy the cause was often acute symptomatic. Stroke was a very prominent cause in cases without previous epilepsy. Outcome was mainly determined by the cause of SPSE; this was true for all 4 patients who died and for 6 of 10 patients with morbidity. In one patient morbidity (aphasia) after SPSE was considered to be caused by SE itself. Outcome could not be related to duration of SE; therapy was more often inadequate in cases with morbidity or mortality.

11.3 Results in children (chapter 7 and 8)

We discussed SE in children separately from adults because of known differences in causes and outcome in comparison to adult patients. We studied 82 children with GCSE (table 2). Acute symptomatic causes were rare in children with previous epilepsy; previous epilepsy was especially present in children older than 1 year, which is in accordance with the literature. Outcome in children of less than 1 year was worse than in older children and outcome in children without previous epilepsy was far worse than in patients with previous epilepsy, both reflecting the contribution of acute symptomatic causes.

Apart from the underlying cause, we have shown that a longer duration, the presence of more than one medical complication and inadequate therapy may contribute to a worse outcome.

Children without medical complications may die because of SE itself, although this was the case in only 1.8%. The relation between outcome and medical complications in children has not been reported before; especially deleterious were respiratory insufficiency and intra-cranial hypertension. Therapy was inadequate in two children with morbidity because of SE and in none of those who died because of SE.

Table 2: Outcome of GCSE in children

Outcome in children	Good	Morbidity		Mortality	
		Total	SE	Total	SE
GCSE (82)	73.2	13.4	3.7	13.4	6.1
Previous epilepsy (51)	84.3	5.9	1.9	9.8	7.8
No previous epilepsy (31)	54.8	25.8	6.4	19.4	3.2
GCSE (82)	75.0	12.5	3.7	12.5	6.1
MR (38)	86.9	5.2	2.6	7.9	7.9
No-MR (44)	61.4	20.5	4.5	18.2	4.5
GCSE at the ICU (35)	42.8	25.7	2.9	31.4	8.6
Previous epilepsy (14)	42.9	21.4	0	35.7	22.2
No previous epilepsy (21)	42.8	28.6	3.8	28.6	3.8
GCSE non-ICU					
Total (47)	95.7	4.3	0	0	0

* GCSE: generalized convulsive SE; MR: mental retardation; ICU: intensive care unit; non-ICU: not admitted at the ICU.

Prognosis of *NCSE* in children was favourable in most cases; CPSE was present in 15 patients, typical ASE in only two and atypical ASE in six. Most children with CPSE were known with previous epilepsy (12).

During our study we came across some children with cognitive deterioration and electrical status epilepticus during sleep, Continuous Spikes and Waves during Sleep (CSWS) and acquired aphasia or Landau-Kleffner syndrome (LKS). The diagnosis in clinical practice is often difficult and treatment disappointing. In all the children in our group a plausible link could be made between cognitive regression and the EEG disturbances during sleep. CSWS or LKS could also be present without clinically manifest seizures. In contrast to information from the literature, aggravation of clinical seizures did not occur and treatment with first line drugs (valproate and/or benzodiazepines) was without any effect on cognition. With such a small group it was difficult to discuss the relation between prognosis and duration of CSWS or severity of epilepsy. It was, however, striking that duration of CSWS in this group was relatively long and cognitive prognosis of most of the children poor. Prognosis appeared more favourable when the age of onset was more than 9 years. The treatment of this syndrome is not

simple, both from a medical point of view and with regard to the serious behavioural problems. Good results are best achieved by a multidisciplinary approach within a specially adapted treatment environment. If this condition is not recognised or is neglected it may result in irreversible damage with serious cognitive and behavioural problems. An EEG during sleep must be made when children have an unexplained cognitive regression.

11.4 Results in patients with mental retardation (chapter 9)

We have performed a retrospective study of SE in MR to investigate whether specific features were present, which were different from SE in the population without MR. We were particularly interested in causes and outcome of the various types of SE in MR.

We discussed the results in 113 adults and 57 children with MR and SE. GCSE was the most frequent type of SE in both adults (81,4%) and children (66,7%) with MR, which is in accordance with the literature. NCSE was present in a larger group of children (29,8%) than in adult patients (7,1%). EPC and NCSE did not occur in the elderly group. The diagnosis of SE appeared wrong in eight adults, presumed to have had GCSE. The group of patients with MR and GCSE was characterized by the high percentage of previous epilepsy. Previous epilepsy was present in 98,2% of both the adults and the children with GCSE. In only two adults and one child an acute symptomatic cause was present. Causes of GCSE in adults included low levels of AED (24%) and systemic infections (4,3%), but in the majority the cause of SE remained unknown (69,5%). Outcome in GCSE did not differ from cases with previous epilepsy without MR (table 1 and 2). One should take into account that minor cognitive decline after GCSE in patients with MR cannot be ruled out. Several factors that may contribute to outcome in GCSE were investigated. The underlying cause as the main factor with respect to outcome could not be acknowledged, because most of the patients were known with previous epilepsy and showed a low number of acute symptomatic causes. Our study could not find a relation between duration of GCSE or the quality of therapy and outcome. The presence of one or more medical complications was related to poor outcome, especially in children. The relation between outcome and SE itself was evident in six adults and

four children. Morbidity because of SE itself was present in 4,3% of the adults with MR and in 2,6% of the children; mortality in adults because of SE itself was 2,2% and in children 7,9%. In children no differences were found between cases with or without MR with respect to the contribution of SE itself to outcome. In adults more patients without MR died because of SE itself (7,5%) than adults with MR (2,1%); the rates of morbidity because of SE itself were comparable in adults (table 1).

This study has demonstrated that patients with MR and SE, who had to be admitted to a hospital, showed comparable outcome to patients without MR but with previous epilepsy. These more complicated cases of SE in patients with MR have a favourable outcome, provided that medical complications are anticipated and properly treated.

11.5 Results of patients with GCSE treated at the ICU (chapter 10)

Most patients with SE (80-85%) are treated adequately with benzodiazepines (BDZ) and/or phenytoin (PHT). SE refractory to these drugs is frequently caused by an acute neurological insult. Admission to the Intensive Care Unit (ICU) may be necessary especially when medical complications, such as respiratory insufficiency, are present, or when anaesthesia is mandatory. Few studies describe cohorts of patients with SE admitted to the ICU (Goulon et al, 1985; Nouailhat et al, 1985; Barois et al, 1985; Lacroix et al, 1994; Erikkson and Koivikko, 1997; Holtkamp et al, 2005). A drawback of these studies was the inclusion of different types of SE. Most patients admitted to the ICU because of SE are not known with previous epilepsy; they show a large percentage of acute neurological insults and a high morbidity and mortality rate. Outcome is especially determined by the underlying cause.
We studied 110 adults and 35 children admitted to the Intensive Care Unit because of Generalized Convulsive Status Epilepticus (GCSE). Causes of GCSE in adult patients with previous epilepsy were non-compliance and systemic infections, in children systemic infections. Acute symptomatic causes in adult patients without previous epilepsy were stroke, intoxication, metabolic disturbances and brain tumours; in children the main causes were bacterial meningitis and viral encephalitis. In comparison to cases with

GCSE not admitted to the ICU outcome was worse. Cause and the number of medical complications especially determined outcome. Especially in children more severe cases with GCSE occurred, which caused a significantly worse outcome in children with previous epilepsy.

We confirmed the less favourable outcome in the very young child or in the older age group and in patients without previous epilepsy. Causes and precipitating factors were not very different from other reports. The number of patients with previous epilepsy and an acute symptomatic cause (4.5%) was not very different from the total group of patients with previous epilepsy (5.9%). Causes with a poor outcome were CVA and cardiac arrest in adult patients and in children resuscitation after laryngo-bronchitis and hypoxia and pneumococcal meningo-encephalitis. Outcome in adult cases with previous epilepsy was better than without previous epilepsy (table 1), this was not the case in children (table 2). Outcome in cases not admitted to the ICU was better, with less morbidity and mortality because of SE itself (table 1). This may indicate that patients with GCSE admitted to the ICU are more severe cases of SE, especially in children. EEG monitoring at the ICU is important, especially in cases that have been paralysed (mechanical ventilation), but also to adjust therapy. With the help of simultaneous recording of the EEG and ICP-monitoring we have observed a relation between seizures and the subsequent rise of ICP, which has been reported earlier (Gabor et al, 1984; Tsementzis et al, 1979). ICP monitoring may also have important therapeutic consequences, especially when cerebral perfusion pressure reaches a critical threshold.

Outcome in patients admitted to the ICU because of GCSE is worse than in cases not admitted to the ICU. Apart from serious acute symptomatic causes, the severity of SE appeared also important with respect to outcome, stressing the importance of treatment according to protocol.

11.6 Conclusions

This study has several drawbacks, related to the retrospective nature. However, in comparison to other retrospective studies, it provided more adequate information with respect to the differentiation in age groups,

types of SE and the presence of previous epilepsy or not. We discussed outcome not only in relation to the type of SE, the presence of previous epilepsy or not, but also in relation to duration of SE, the presence of medical complications or not and the quality of treatment, which has not been subject of earlier studies. The number of patients of our study was sufficient to make suggestions how to improve the care of difficult to treat cases with SE, taken into account the results of outcome and the various contributing factors in this respect. This descriptive study has been able to make clear that outcome of the various types of SE is especially determined by its cause, but also that outcome may improve, provided that one takes notice of medical complications and adequate treatment. These findings promote therapy according to protocol, with special emphasis on duration, potential lethal medical complications and adequate therapy. An example of such a protocol has been discussed and presented in chapter 3.9. This protocol has been the basis of later directives, developed by a study group of the association of the Dutch neurologists (Donselaar et al, 2001).

Some indices of severity may be introduced, which have been determined by known contributing factors to outcome (table 3). It is known and acknowledged by our results that prognosis of ASE is always good; the index of severity will be zero for this type of SE. Prognosis for GCSE may be unfavourable, so the index will be two. In this way one can discuss the indices for the presence of an acute symptomatic cause or not, the presence of previous epilepsy or not, duration of SE and the start of treatment. After admission of a patient with SE the various indices may be determined, which may promote prompt admission to the ICU and treatment according to protocol especially in cases with a severity index of more than 4.

Table 3: Indices of severity

	0	1	2
Type of SE	ASE	CPSE SPSE	GCSE
Number of medical complications	None	1	>1
Acute symptomatic cause	Not present	–	Present
Previous epilepsy	Present	Not present	–
Duration of SE	< 60 min	60-120 min	>120 min
Start of treatment	Within 30 min	–	After 120 min

Our study is unique in the Netherlands. Until now only some case reports have been published, regarding GCSE (Frederiks, 1969; Hootsmans, 1954; Lorentz De Haas, 1960; Verjaal and Goor, 1969; van Huffelen, 1983), ASE (Visser, 1970), SPSE with aphasia as the main symptom (Jongsma and Vanneste, 1991), CPSE (Storm and Casteelen, 1999), the Landau-Kleffner Syndrome (Stroink et al, 1997) and treatment of SE with clonazepam (van Huffelen and Magnus, 1976). The importance of a treatment protocol has been stressed in one review in the Dutch medical literature, based on a foreign symposium (van Huffelen, 1983).

Our study has shown that gaps are present in the knowledge about adequate treatment of SE, but also in the recognition of the various types of SE. The results of this study may contribute to fill these gaps, and call for further prospective investigations, with specific attention to the elderly and patients with mental retardation. The reason for the specific attention is that it is very likely that many cases of SE, especially NCSE, have not been recognized as such in the elderly and patients with MR. With the current economy less attending personnel will be available, with obvious implications for the care of patients with epilepsy and/or some type of SE. Also, the current possibilities for proper coding of the various types of SE are not sufficient, which may contribute to inadequate registration.

The Netherlands is a small country with an excellent healthcare and an adequate relation between the number of physicians and the number of inhabitants. Considering the number of inhabitants one may expect a high number of new cases with SE every year. Foreign prospective studies suggest at least 3000 cases of SE, possibly even higher (6000-10000). These numbers would suggest that in a local hospital SE would be diagnosed in

at least 2-4 patients every month, which will appear unexpectedly high to many neurologists in the Netherlands. These foreign numbers even do not include a considerable number, which could not be ascertained. That is why it would be very important to find out the true incidence of the various types of SE in the Netherlands, with special emphasis on morbidity and mortality. Prospective investigations will require adequate cooperation between neurologists, general practitioners, physicians taking care of patients with mental retardation and psychiatrists. In some parts of the USA 24 hour SE-teams are available for diagnosis and treatment of all patients with the various types of SE. Such an approach offers many advantages for prospective studies, although the problem of under-ascertainment will not be completely solved (DeLorenzo et al, 1996). A prospective study offers possibilities for further investigation on the various aspects of SE in the Netherlands, including incidence. A major subject should be a prospective trial of treatment of SE, when first line drugs fail; information on this subject is not available, not only in the Netherlands, but also not abroad.

Several centres in the Netherlands have proven to be able to perform and present excellent research in other fields of epileptology. That is why the situation in the Netherlands provides ideal opportunities for prospective studies of various aspects of SE, such as:

- The incidence of the various types in the general population, the elderly or in patiënts with MR.
- Trials of treatment of refractory SE.
- The consequences of NCSE in MR.
- Cognitive consequences of SE in various clusters of patients.
- Neuro-imaging studies that may contribute to the knowledge about pathophysiology of SE and the discussion about the definition of SE.

Considering the recent developments in finance of the Dutch healthcare with the introduction of Diagnose Behandel Combinaties (DBC), it is essential to provide separate DBC-codes for SE. Treatment of patients with SE may take considerable time and effort, and involve considerable expense due to drugs and potential ICU-care (Penberthy et al, 2005). Separate codes for SE will also contribute to improvement of registration.

Samenvatting en bespreking

Inleiding

Deze studie werd geboren uit frustraties die ontstonden tijdens de behandeling van patiënten met status epilepticus (SE), welke niet reageerden op de gebruikelijke eerste keus middelen, zoals diazepam en/of fenytoine en waarbij de behandeling vaak willekeurig bleek te verlopen. Ook op de Intensive Care Unit (ICU) van een academisch ziekenhuis verliep de behandeling van SE niet of nauwelijks geprotocolleerd en er werd weinig rekening gehouden met de pathofysiologie van SE. Dat was niet alleen het geval in dat academisch ziekenhuis, doch gezien de bevindingen bij patiënten welke uit andere ziekenhuizen werden overgenomen, ook elders. Ervaringen met enkele ernstige gevallen van SE resulteerde in een eerste versie van een therapieprotocol (Scholtes en Dries, 1986) en de start van een retrospectief onderzoek naar de aanpak in andere ziekenhuizen in Nederland.

Ten tijde van het begin van de studie waren er geen gegevens bekend over de diverse aspecten van SE in Nederland, zoals de oorzaken, de incidentie en prevalentie, de medische complicaties welke kunnen optreden, de behandeling, de morbiditeit en de mortaliteit. Er waren enkele studies gepubliceerd door Nederlandse auteurs, welke voornamelijk afzonderlijke patiënten betroffen met een bepaald type SE, zoals GCSE (Frederiks, 1969; Hootsmans, 1954; Lorentz De Haas, 1960; Verjaal and Goor, 1969; van Huffelen, 1983), ASE (Visser, 1970), en behandeling van SE met clonazepam (van Huffelen and Magnus, 1976). Er was slechts één overzichtsartikel gepubliceerd over de behandeling van SE volgens protocol, overigens gebaseerd op een buitenlandse conferentie over dit onderwerp (van Huffelen, 1983). De buitenlandse literatuur op dat moment bestond voornamelijk uit retrospectieve en selectieve studies met patiënten uit universiteitsklinieken of gespecialiseerde centra. Deze studies hadden, naast het retrospectieve karakter zelf, diverse nadelen:

1. Grote verschillen in de duur van de follow-up.
2. Het bespreken van de resultaten zonder een onderscheid te maken in type SE of leeftijdsgroep.
3. Geen onderscheid in patiënten die al bekend waren met epilepsie of niet.
4. Geen onderscheid in morbiditeit/mortaliteit ten gevolge van de onderliggende oorzaak of SE zelf.

Recente prospectieve studies hebben deze nadelen niet helemaal kunnen verhelpen (DeLorenzo et al, 1996; Knake et al, 2001). Zo werd bijvoorbeeld mortaliteit nog steeds vermeld los van het type SE, terwijl bekend was dat de resultaten bij complex partiële SE (CPSE) over het algemeen gunstiger zijn dan bij gegeneraliseerde convulsieve SE (GCSE).
Incidentiegegevens waren ten tijde van de aanvang van de studie beperkt tot schattingen; enkele recente studies hebben hierover wel prospectieve gegevens kunnen verstrekken (DeLorenzo et al, 1996; Coeytaux et al, 2000; Knake et al, 2001)

We begonnen de gegevens te verzamelen van zoveel mogelijk patiënten met SE opgenomen in diverse ziekenhuizen en epilepsiecentra in Nederland in de periode 1980-1987. Patiënten werden alleen in de studie opgenomen indien zij voldeden aan de gangbare definitie van SE. Ten einde de patiënten te kunnen opsporen werd gebruikt gemaakt van de registratie van de ontslagdiagnose, gecodeerd volgens de ICD-9, zoals die werd gehanteerd door de ziekenhuizen in Nederland en door de SIG, Stichting Informatievoorziening Gezondheidszorg. Deze codering heeft echter beperkingen, er kunnen slechts drie typen SE worden geregistreerd: petit mal SE (code 345.2), grand mal SE (code 345.3) en EPC (code 345.7). Een aparte code voor CPSE of tonische SE is er gewoon niet. We vonden overigens diverse gevallen met CPSE, terwijl de ontslagcode heel anders was, zoals petit mal SE of zelfs grand mal SE.

Tijdens het onderzoek werden diverse problemen gesignaleerd:

1. Onvoldoende coderingsmogelijkheden voor de diverse typen SE.
2. Onjuiste ontslagdiagnosen (20%).
3. Het voorkomen van een onjuiste classificatie van het type SE.
4. De duur van SE kon niet altijd worden achterhaald. De duur werd in dit soort gevallen geschat op basis van informatie over transport naar het ziekenhuis en/of duur behandeling.
5. Informatie over behandeling door huisarts of ambulance personeel bleek schaars.
6. Niet alle geregistreerde gevallen konden worden opgespoord.
7. Gevallen met SE gezien in consult op andere dan neurologische afdelingen waren niet of nauwelijks op te sporen.

De registratie van de patiënten met SE vertoonde nogal grote verschillen in zorgvuldigheid per ziekenhuis. De kleinere ziekenhuizen bleken hierbij de minste fouten te scoren en vertoonden ook de minste hoeveelheid patiënten met een onjuiste diagnose van SE (No-SE). Een protocol voor de behandeling van SE was slechts aanwezig in één academisch ziekenhuis en een epilepsiecentrum. Dat betekende overigens niet dat dit protocol dan ook gevolgd werd. Andere onderzoekers hebben ook melding gemaakt van het gegeven dat de diagnostiek van epileptische aanvallen of van SE in de praktijk problemen kan opleveren; SE werd niet herkend of de diagnose bleek incorrect in een relatief groot aantal van de patiënten (Handforth et al, 1993; Garnett et al, 1994; Berger et al, 1999). De onderzoekers beklemtoonden het belang van de aanwezigheid van een neuroloog of van een 24-uur SE-Team in deze soms complexe situaties. De problemen welke wij tegenkwamen, zoals het aantal gevallen No-SE, zijn dus deels herkenbaar uit andere studies.

Verschillende studies hebben een poging gedaan het voorkomen van SE in diverse populaties te onderzoeken. Deze studies waren tot voor kort voornamelijk retrospectief, met alle daar aan gekoppelde nadelen. Daarnaast moet men echter ook aan andere problemen denken:

- De diagnose SE is in de praktijk niet altijd makkelijk te stellen.
- De diagnose SE wordt niet altijd overwogen, met name niet NCSE bij verstandelijk gehandicapten of bij patiënten met verwardheid.
- Een aantal patiënten worden buiten het ziekenhuis behandeld.
- SE bij patiënten, opgenomen vanwege een ander medisch probleem, wordt vaak niet als zodanig geregistreerd.
- Duur van de aanvallen wordt niet altijd vastgelegd; korte perioden SE kunnen dan als aanvallen worden geregistreerd, niet als SE.
- In de klinische praktijk wacht men niet met de behandeling tot men voldoet aan de definitie; veelal begint men na een aanvalsduur van 5-10 minuten, bij een excacerbatie van een patiënt bekend met epilepsie of bij een serie aanvallen. Een onjuiste ontslagdiagnose SE is hierbij niet zeldzaam.

Recente prospectieve studies hebben ook melding gemaakt van het probleem dat een groot aantal van de gevallen met SE niet te achterhalen zijn (DeLorenzo et al, 1995; Knake et al, 2001). Ook bij prospectieve studies

zullen dus veel gevallen niet worden vastgelegd. Daarnaast is er dus ook nog het probleem van de codering. Het zal dus duidelijk zijn dat het erg moeilijk is alle gevallen met SE in een bepaald jaar op te sporen.
Onze studie heeft belangrijke informatie opgeleverd, welke in de literatuur, ook de recente, niet aanwezig is:

- Verschillen in resultaat bij patiënten bekend met of zonder epilepsie.
- Oorzaken SE in patiënten bekend met of zonder epilepsie.
- De relatie tussen resultaat en de aanwezigheid van medische complicaties.
- De relatie tussen resultaat en duur SE.
- De relatie tussen resultaat en de behandeling van SE.
- De relatie tussen resultaat en onderliggende oorzaak dan wel de gevolgen van SE zelf.
- Informatie over SE in verstandelijk gehandicapten.

Met onderkenning van de beperkingen werd getracht informatie te verzamelen over patiënten die vanwege SE in een ziekenhuis moesten worden opgenomen. Wij gingen er hierbij vanuit dat een patiënt met SE in een ziekenhuis werd opgenomen en geregistreerd door het SIG. Niet alle gevallen zullen echter worden geregistreerd. Gebaseerd op de gegevens van het SIG werd, in overleg met Dr. G. Zielhuis van het instituut voor epidemiologie, aangenomen dat een aantal van 500 gevallen met SE voldoende zou zijn om de verschillende vragen van de studie te kunnen beantwoorden. Van in totaal 576 volwassenen en 112 kinderen, afkomstig uit 12 ziekenhuizen en 2 epilepsie-centra konden gegevens geëvalueerd worden.

Resultaten bij volwassenen (hoofdstuk 4-6)

Opvallend was het gegeven dat de diagnose SE in 20% van de gevallen, als zodanig gerapporteerd aan het SIG, niet correct was (tabel 1).

De onderliggende oorzaak bleek de belangrijkste bepalende factor te zijn met betrekking tot het uiteindelijk resultaat van de behandeling van GCSE. Dit bleek bijvoorbeeld uit het feit dat de resultaten bij patiënten bekend met epilepsie vergelijkbaar waren met die van patiënten zonder epilepsie, indien de oorzaak van GCSE acuut symptomatisch was. De resultaten van patiënten waarbij de diagnose SE incorrect (No-SE) bleek te zijn, waren vergelijkbaar met die van patiënten bekend met epilepsie uit de totale

groep SE en uit de groep GCSE (tabel 1). De morbiditeit en de mortaliteit in de No-SE groep werd geheel bepaald door een specifieke oorzaak, zoals CVA, hersentumor, trauma capitis of encephalitis. De totale morbiditeit en mortaliteit in de gehele groep SE, alsmede in de GCSE groep bleek hoger dan in No-SE, waarbij men zou kunnen concluderen dat de aanwezigheid van SE zelf een negatieve bijdrage levert aan het uiteindelijke resultaat. Dit kan ook beïnvloed worden door de aanwezigheid van meer ernstige acuut symptomatische pathologie in de SE groep of door beiden.

Tonisch-clonische SE (TCSE) is de meest voorkomende vorm van GCSE en van alle typen SE. Recente prospectieve studies suggereren een incidentie van TCSE van 5-30 per 100.000 (DeLorenzo et al, 1996; Coeytaux et al, 2000; Knake et al, 2001). Dit betekent per jaar tenminste 1000 gevallen van TCSE in Nederland.

De resultaten van 346 opnamen vanwege GCSE bleken negatief te worden beïnvloed door de aanwezigheid van een acute symptomatische oorzaak, maar ook door de aanwezigheid van meer dan 1 medische complicatie, door een duur van SE van meer dan 4 uur en door een inadequate behandeling. De invloed van deze laatste 3 factoren was met name duidelijk indien SE zelf verantwoordelijk was voor de morbiditeit of mortaliteit. Enkele medische complicaties, zoals respiratoire insufficiëntie, bleken schadelijker te zijn dan anderen. Ook werden gevallen beschreven welke overleden aan de gevolgen van SE zelf, terwijl er geen medische complicaties aanwezig waren. Dit gebeurde overigens niet vaak (1-2%). De oorzaken van TCSE waren vergelijkbaar met die uit de literatuur.

De behandeling van GCSE bestond voornamelijk uit benzodiazepines en\ of fenytoine. De resultaten in de grotere ziekenhuizen waren minder gunstig dan in de kleinere of de epilepsiecentra, hetgeen samenhing met het hogere percentage acute symptomatische oorzaken en medische complicaties.
Indien men de resultaten van recente prospectieve studies extrapoleert op Nederland, dan kan per jaar ongeveer een aantal van 636 volwassenen met TCSE worden verwacht (Knake et al, 2001). Vanuit dit getal en onze resultaten m.b.t. de kwaliteit van de behandeling kan worden berekend dat per jaar 10 gevallen met morbiditeit en 24 doden kunnen worden vermeden, indien de behandeling wel adequaat verloopt. Hierbij kan een protocol een ondersteuning bieden.

Tabel 1: Resultaten status epilepticus (SE) bij volwassenen per type*

Resultaten bij volwassenen	Goed	Morbiditeit		Mortaliteit	
		Totaal	SE	Totaal	SE
No-SE (118)	86.4	5.1	–	8.5	–
Bekend met epilepsie (69)	91.3	1.4		7.2	
Niet bekend epilepsie (41)	78.0	12.2		9.8	
SE totaal (458)	76.0	14.7	4.8	9.5	5.1
Bekend epilepsie (314)	87.0	6.4	3.8	6.4	3.5
Niet bekend epilepsie (144)	57.0	19.8	2.1	22.6	8.5
GCSE (346)	76.0	13.0	3.5	11.0	6.1
Bekend epilepsie(236)	85.5	8.5	3.8	6.0	4.3
Niet bekend epilepsie(110)	55.5	22.7	2.7	21.8	9.9
GCSE (346)					
MR (92)	87.0	8.7	4.3	4.3	2.2
No-MR (254)	72.0	14.6	3.1	13.4	7.5
No-MR bekend epilepsie (144)	84.7	8.3	3.5	6.9	5.6
No-MR niet bekend epilepsie (110)	55.9	22.5	2.7	21.6	9.9
GCSE					
Opname ICU (110)	56.3	20.9	4.5	22.7	11.8
Bekend epilepsie (66)	66.7	15.1	7.5	18.2	16.6
Niet bekend epilepsie (44)	40.9	29.5	0	29.5	4.5
Non-ICU (246)	82.7	9.6	2.8	7.6	3.6
CPSE (40)	80.0	15.0	2.5	5.0	2.5
Bekend epilepsie (28)	96.4	0	0	3.5	3.5
Niet bekend epilepsie (12)	41.6	50.0	8.3	8.3	0
ASE (25)	100	0	0	0	0
SPSE (47)	70.2	21.3	2.1	8.5	0
Bekend epilepsie (27)	85.2	14.8	3.7	0	0
Niet bekend epilepsie (20)	50.0	30.0	0	20	0

* SE. No-SE: onjuiste diagnose SE. GCSE: gegeneraliseerde convulsieve SE; MR: mentale retardatie (verstandelijke handicap); ICU: intensive care unit; non-ICU: niet opgenomen in ICU; CPSE: complex partiële SE; ASE: absence SE; SPSE: simpele partiële SE.

De diagnostiek van *NCSE* blijkt in de klinische praktijk niet altijd eenvoudig en zelfs niet altijd overwogen. Een prospectief onderzoek in Zwitserland, met 24 uur mogelijkheden voor EEG registratie, vond een incidentie van

4.4 per 100.000 (Coeytaux et al, 2000). Andere onderzoekers vonden lagere cijfers, doch onderkenden het probleem dat niet alle gevallen te achterhalen zijn (Tomson et al, 1992; DeLorenzo et al, 1996). Op basis van de gegevens uit Zwitserland kan men per jaar in Nederland 700 gevallen verwachten met CPSE en 96 met ASE.

Patiënten met NCSE werden, zoals gebruikelijk in de literatuur, verdeeld in gevallen met ASE en CPSE. Een probleem bleek het feit dat niet in alle gevallen van CPSE een EEG werd verricht. De diagnose werd gesteld op basis van het klinisch beeld, de voorgeschiedenis en het resultaat van de behandeling. De groep bestond uit 40 gevallen met CPSE en 25 met ASE.

Alle patiënten met ASE hadden een goed resultaat, ondanks dat de behandeling niet altijd adequaat genoemd kon worden. De oorzaken van ASE bleken vergelijkbaar te zijn met die uit de literatuur.

De morbiditeit van *CPSE* werd met name bepaald door de onderliggende oorzaak. Bij één patiënt werd aannemelijk gemaakt dat de persisterende geheugenstoornis na CPSE veroorzaakt werd door de ontladingen zelf. Er was een groot verschil in resultaat tussen patiënten met of zonder epilepsie (tabel 1). Alle patiënten met CPSE bekend met epilepsie hadden een goed resultaat, één uitgezonderd. Deze oudere patiënt overleed aan de gevolgen van aspiratie-pneumonie, welke hij had opgelopen tijdens CPSE.

Een relatie met de duur van SE of de behandeling kon niet worden aangetoond. De therapie was in gevallen met morbiditeit niet altijd adequaat; in drie gevallen heeft dit bijgedragen aan het resultaat.

De behandeling van CPSE verliep in de diverse ziekenhuizen erg wisselend en was vaak inadequaat. In gevallen met langdurige CPSE dient men rekening te houden met mogelijke morbiditeit als gevolg van de ontladingen zelf. MRI onderzoek kan hierbij meer informatie verschaffen en bijdragen aan de discussie rond de behandeling van CPSE.

SPSE is relatief zeldzaam. De eerder genoemde prospectieve studies suggereren een aantal van ongeveer 480 patiënten per jaar in Nederland. Uit ons onderzoek bleek dat de diagnose niet altijd correct gesteld was. Onze groep van 47 is een van de grootste in de literatuur. Ten opzichte van de gegevens uit de literatuur vonden wij een hoger percentage vrouwen, een kortere duur en een hoger percentage patiënten die reeds epilepsie hadden. Met uitzondering van 1 patiënt met afasie als uiting van partiële SE hadden alle

andere een somato-motore expressie. Tussen de continue vorm (EPC) en die in aanvallen was geen verschil m.b.t. de kliniek, oorzaken of het resultaat van de behandeling. Een belangrijke bevinding was het feit dat in 20% van de gevallen die al bekend waren met epilepsie, een nieuw medisch probleem (tumor, CVA) verantwoordelijk was voor de SPSE. Bij patiënten niet bekend met epilepsie bleek CVA de meest voorkomende oorzaak te zijn van SPSE. De resultaten werden grotendeels bepaald door de oorzaak. Bij 1 patiënt bleek dat SE zelf verantwoordelijk was voor de morbiditeit (afasie).

Resultaten bij kinderen (hoofdstuk 7 en 8)

De diverse typen SE werden bij 112 kinderen beschreven in de leeftijd van 28 dagen tot 15jaar. *GCSE* (82) bleek de meest voorkomende vorm van SE te zijn. De resultaten van GCSE werden met name bepaald door de oorzaak. Andere factoren waren de duur en de aanwezigheid van medische complicaties (>1), terwijl de kwaliteit van de behandeling niet duidelijk scoorde.

De resultaten bij kinderen jonger dan 1 jaar bleken minder gunstig dan die bij oudere kinderen, hetgeen gerelateerd was aan het frequenter voorkomen van acuut symptomatische oorzaken bij het jonge kind. Ook kinderen zonder medische complicaties konden door SE zelf overlijden, hoewel dit weinig voorkwam (1.8%).

De relatie met medische complicaties werd tot nu toe niet beschreven bij kinderen; de meest schadelijke waren respiratoire insufficiëntie en intracraniële drukverhoging.

In de groep met *NCSE* (27) hadden 15 kinderen *CPSE*, 2 typische en 6 atypische *ASE*. De meeste kinderen met CPSE waren bekend met epilepsie. De resultaten bij NCSE waren veelal goed; 1 patiënt vertoonde na CPSE een lichte afasie.

De resultaten bij 7 kinderen met *CSWS* en 3 met *Landau-Kleffner syndroom* (LKS) waren ongunstig; slechts 1 kind vertoonde een compleet cognitief herstel. Dit leek samen te gaan met een lange duur van het ESES patroon in de slaap. De prognose bleek gunstiger bij een debuutleeftijd van meer dan 9 jaar. Niet alle kinderen met CSWS of LKS waren bekend met epilepsie. De behandeling met eerste keus middelen als valproaat of benzodiazepines bleek in de meerderheid in het geheel niet aan te slaan. Bij kinderen met onbegrepen cognitieve achteruitgang dient EEG onderzoek in de slaap te gebeuren.

Resultaten bij verstandelijk gehandicapten (hoofdstuk 9)

Het onderzoek van SE bij de verstandelijk gehandicapten (VG) was er op gericht na te gaan of er bij deze doelgroep specifieke kenmerken aanwezig waren die anders waren t.o.v. de doorsnee bevolking. Ook bij VG was *GCSE* de meest voorkomende vorm, bij zowel volwassenen als kinderen. De grote meerderheid met GCSE bleek tevoren al bekend te zijn met epilepsie (98,2%). Een acute symptomatische oorzaak was slechts aanwezig bij twee volwassenen en een kind. De resultaten bij GCSE waren vergelijkbaar met patiënten zonder VG, indien bekend met epilepsie (tabel 1). Eventuele discrete cognitieve achteruitgang kan bij deze doelgroep niet uitgesloten worden, dit valt in de praktijk minder op dan bij mensen zonder VG. De resultaten werden negatief beïnvloed door de aanwezigheid van 1 of meer medische complicaties, met name bij kinderen. Een relatie met de duur van SE of de kwaliteit van de behandeling kon niet worden aangetoond. Bij volwassenen zonder VG overlijden meer patiënten (7.5%) aan de gevolgen van SE zelf dan volwassenen met VG (2.1%). De resultaten bij VG lijken niet ongunstig, zeker als men aanneemt dat het de meer gecompliceerde gevallen zullen zijn, daar een behoorlijk aantal behandeld wordt in hun eigen woonomgeving. De resultaten kunnen verder verbeterd worden door betere aandacht voor de medische complicaties.

Tabel 2: Resultaten GCSE in kinderen*

Resultaten bij kinderen	Goed	Morbiditeit		Mortaliteit	
		Totaal	SE	Totaal	SE
GCSE (82)	73.2	13.4	3.7	13.4	6.1
Bekend epilepsie (51)	84.3	5.9	1.9	9.8	7.8
Niet bekend epilepsie (31)	54.8	25.8	6.4	19.4	3.2
GCSE (82)	75.0	12.5	3.7	12.5	6.1
MR (38)	86.9	5.2	2.6	7.9	7.9
No-MR (44)	61.4	20.5	4.5	18.2	4.5
GCSE in de ICU (35)	42.8	25.7	2.9	31.4	8.6
Bekend epilepsie (14)	42.9	21.4	0	35.7	22.2
Niet bekend epilepsie (21)	42.8	28.6	3.8	28.6	3.8
GCSE non-ICU					
Totaal (47)	95.7	4.3	0	0	0

* GCSE: gegeneraliseerde convulsive SE; MR: mentale retardatie (verstandelijke handicap); ICU: intensive care unit; non-ICU: niet opgenomen in ICU.

GCSE in de Intensive Care Unit (hoofdstuk 10)

De meeste patiënten met SE kunnen goed worden behandeld met benzodiazepines en/of fenytoine. Opname in de ICU kan nodig zijn vanwege medische complicaties, zoals respiratoire insufficiëntie, of wanneer anesthesie nodig is. Er zijn enkele studies bekend die patiënten beschrijven die vanwege SE behandeld werden op de ICU (Goulon et al, 1985; Nouailhat et al, 1985; Barois et al, 1985; Lacroix et al, 1994; Erikkson and Koivikko, 1997; Holtkamp et al, 2005). Een nadeel van deze studies is dat men verschillende types door elkaar heen beschrijft, hetgeen de resultaten moeilijk beoordeelbaar maakt.

We konden de resultaten bestuderen bij 110 volwassenen en 35 kinderen die vanwege GCSE moesten worden opgenomen in de ICU. Oorzaken bij volwassenen, bekend met epilepsie waren non-compliance en algemene infecties; bij kinderen voornamelijk algemene infecties. Bij volwassenen, niet bekend met epilepsie vonden we CVA, intoxicaties, metabole stoornissen en hersentumoren; encephalitis en meningitis waren bij kinderen frequente oorzaken. De minder gunstige resultaten bij het jonge kind, bij ouderen en bij patiënten niet bekend met epilepsie kwamen overeen met die uit de literatuur. De oorzaken van GCSE waren vergelijkbaar met eerdere studies. Oorzaken van GCSE met een slechte prognose waren bij volwassenen CVA en hartstilstand, bij kinderen resuscitatie na laryngo-bronchitis, hypoxie en pneumococcen-meningitis. De resultaten bij patiënten die moesten worden opgenomen in de ICU waren minder gunstig dan indien opname in de ICU niet nodig was. Dit had enerzijds te maken met het hoger percentage acuut symptomatische oorzaken, maar ook met de ernst van de GCSE zelf, met name bij kinderen (tabel 1, tabel 2). Dit werd ondersteund door het feit dat de resultaten bij kinderen, bekend met epilepsie, net zo ongunstig waren als die bij kinderen zonder epilepsie. Ook het gegeven dat de morbiditeit en de mortaliteit ten gevolge van SE zelf bij patiënten opgenomen in de ICU hoger zijn dan bij patiënten niet opgenomen in de ICU, ondersteunt deze conclusie. EEG monitoring op de ICU is van belang bij patiënten met GCSE, welke worden beademd en gecurariseerd, ten einde de behandeling adequaat te kunnen vervolgen. Tijdens de behandeling werd EEG monitoring gelijktijdig verricht met intracraniële druk (ICP) monitoring in 5 volwassenen en 10 kinderen met ernstige GCSE, waarbij enkele malen een relatie werd vastgesteld tussen epileptische aanvallen en

stijging van de ICP. Ook werd diverse malen vastgesteld dat de ICP dermate kon stijgen dat de cerebrale perfusie druk (CPP) kritisch werd verlaagd. Dit gegeven heeft consequenties voor de behandeling van ernstige gevallen van GCSE. De onderliggende oorzaak is de belangrijkste bepalende factor ten aanzien van de morbiditeit en de mortaliteit. Daarnaast blijkt dat er op de ICU patiënten worden opgenomen met een meer ernstig verlopende vorm van GCSE, waarbij verbetering van de behandeling in een vroegere fase de uiteindelijke resultaten kan verbeteren.

Slotconclusies

Deze studie heeft een aantal nadelen vanwege het retrospectieve karakter. In vergelijking met andere studies hebben we betere informatie kunnen verschaffen over diverse aspecten van SE, door differentiatie in leeftijdsgroepen, typen SE en de aanwezigheid van epilepsie of niet. De resultaten werden daarnaast ook besproken in relatie tot duur SE, de aanwezigheid van medische complicaties en de kwaliteit van de behandeling. Een dergelijke benadering was hiervoor niet eerder gepubliceerd. Het aantal patiënten dat we konden bestuderen, 576 volwassenen en 112 kinderen, was volgens de epidemioloog Dr.G.Zielhuis voldoende om deze gegevens te bespreken. Een prospectieve studie zou een betere opzet zijn geweest, maar de kwantiteit en de kwaliteit van het materiaal zijn voldoende om conclusies te trekken en aanbevelingen te doen. De Nederlandse literatuur over SE is schaars en bevat weinig eigen materiaal; deze studie vult als zodanig duidelijk een leemte op. Deze beschrijvende studie heeft kunnen aantonen dat de resultaten van de diverse typen SE met name worden bepaald door de onderliggende oorzaak. De morbiditeit en de mortaliteit kunnen worden verlaagd indien men bij de behandeling rekening houdt met de medische complicaties en adequate behandeling. Een snelle en adequate behandeling is en blijft essentieel. Dit kan het beste geschieden door de behandeling volgens protocol te laten verlopen, met aandacht voor de duur, de medische complicaties en adequate keuze voor anti-epileptica. Een voorbeeld van een protocol werd beschreven en besproken in hoofdstuk 3.9. Dit protocol werd de basis van de later ontwikkelde richtlijnen voor de behandeling van SE, opgesteld door de Nederlandse Vereniging voor Neurologie (Donselaar et al, 2001).

Men kan bij de behandeling factoren introduceren welke de ernst van het probleem nader definieert. Zoals uit ons onderzoek is gebleken zijn deze factoren de aanwezigheid van medische complicaties of niet, de oorzaak, bekend zijn met epilepsie of niet, de duur van SE, het moment van de start van de behandeling en het type SE (tabel 3). Het is bekend dat de resultaten van ASE altijd goed zijn. ASE als type SE scoort dan 0 punten. De resultaten van GCSE kunnen ongunstig zijn, vandaar de score 2. Op deze manier worden de diverse risico factoren in een getal uitgedrukt. De ernst van de situatie bij opname bepaalt dan of behandeling volgens protocol moet lopen en opname in de ICU bespoedigd moet worden. Volgens de tabel 3 is dit zeker te adviseren bij een score van 4 of hoger.

Tabel 3: Indicatoren van ernst

Indicator	0	1	2
Type SE	ASE	CPSE SPSE	GCSE
Aantal medische complicaties	Geen	1	>1
Acute symptomatische oorzaak	Niet aanwezig	–	Aanwezig
Bekend epilepsie	Aanwezig	Niet aanwezig	–
Duur SE	< 60 min	60-120 min	>120 min
Start behandeling	Binnen 30 min	–	Na 120 min

Onze studie is uniek in Nederland. Niet eerder werd SE in Nederland zo uitgebreid met zoveel patiënten beschreven. We hebben aangetoond dat er hiaten aanwezig zijn in de kennis omtrent de juiste behandeling van SE, maar ook in de herkenning van verschillende typen SE. De resultaten van ons onderzoek kunnen bijdragen deze hiaten op te vullen en vragen om verdere prospectieve onderzoeken, met speciale aandacht voor ouderen en verstandelijk gehandicapten. Het is namelijk erg aannemelijk dat bij deze twee doelgroepen SE vaak wordt gemist, met name NCSE. Met de huidige economische ontwikkelingen zal minder verzorgend personeel voor hen aanwezig zijn, hetgeen consequenties zal hebben voor de kwaliteit van zorg voor ouderen en verstandelijk gehandicapten met epilepsie of een vorm van SE.

Prospectief onderzoek vergt goede samenwerking van de neurologen met huisartsen, artsen werkzaam in de zwakzinnigenzorg en met psychiaters. In de USA heeft men in bepaalde regio's een 24-uurs-SE-team aangesteld, die op elk moment van de dag beschikbaar is voor de opvang van patiënten met SE, waardoor ook het verzamelen van prospectieve gegevens makkelijker is geworden. Ook met deze aanpak bleek overigens een hoog percentage van de gevallen niet geregistreerd te kunnen worden (DeLorenzo et al, 1996).

Deze studie heeft inzicht kunnen verschaffen in oorzaken van de diverse typen van SE, maar ook in factoren die negatief bijdragen aan de resultaten, zoals een lange duur, meerdere medische complicaties en een inadequate behandeling. Ook heeft deze studie laten zien dat de registratie van ontslagdiagnosen moet verbeteren. Enerzijds klopt de ontslagdiagnose in 20% van de gevallen niet, hetgeen een zorgvuldigheidsprobleem is in de ziekenhuizen, anderzijds kan een relatief vaak voorkomende vorm als CPSE niet eens geregistreerd worden, hetgeen een aanpassing vergt van de ICD-codering.

Nederland is een compacte regio met een uitstekende gezondheidszorg en een goede verhouding tussen het aantal artsen en het aantal inwoners. Er vindt op diverse plaatsen hoogwaardig onderzoek plaats omtrent diverse aspecten van epilepsie. Gezien het aantal inwoners in Nederland kan men elk jaar een hoog aantal gevallen met SE verwachten; prospectieve onderzoeken suggereren een jaarlijks aantal van tenminste 3000 patiënten, waarschijnlijk nog veel meer (6.000-10.000). Dit aantal impliceert dat een plaatselijk ziekenhuis in Nederland elke maand 2-4 gevallen met SE zal zien, hetgeen voor veel neurologen een hoog aantal zal lijken.

Gezien het bovenstaande zijn er voldoende randvoorwaarden aanwezig om diverse vragen over SE aan te pakken. Een belangrijk onderdeel van prospectief onderzoek zou een trial moeten zijn naar de behandeling van SE, niet reagerend op eerste keus middelen. Informatie over dit onderwerp is er niet, ook niet in de buitenlandse literatuur. De situatie in Nederland is ideaal voor prospectieve onderzoeken naar diverse aspecten van SE, waarbij men kan denken aan:

– De incidentie van de diverse typen van SE in de algemene populatie, bij ouderen en bij verstandelijk gehandicapten.
– Trial naar de behandeling van refractaire SE.
– De gevolgen van NCSE bij verstandelijk gehandicapten.

– Cognitieve gevolgen van SE in diverse clusters van patiënten.
– Neuro-imaging studies welke kunnen bijdragen aan de kennis van de pathophysiologie van SE en aan de discussie over de definitie van SE.

De huidige ontwikkelingen in de financiering van de gezondheidzorg hebben Diagnose Behandel Combinaties (DBC's) naar voren gebracht, maar er is geen aparte DBC-code voor SE. Men moet hierbij echter bedenken dat de behandeling van SE zeer arbeidsintensief kan zijn, met veel extra kosten voor medicatie en behandeling op de ICU (Penberthy et al, 2005). Een aparte code voor SE is hiermee een logische stap, hetgeen ook een ondersteuning kan zijn voor de registratie van het aantal gevallen met SE.

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List of abbreviations

AED	Anti-epileptic drugs
ASE	Absence Status Epilepticus
BDZ	Benzodiazepines
CBF	Cerebral Blood Flow
CBS	Centraal Bureau voor de Statistiek (Central Bureau of Statistics)
CMR-gluc	Cerebral Metabolic Rate for glucose
CMR-O2	Cerebral Metabolic Rate for Oxygen
CPK	Creatine Phosphokinase
CPSE	Complex Partial Status Epilepticus
CSF	Cerebro-spinal fluid
CSWS	Continuous Spikes and Waves during Sleep
CVA	Cerebral Vascular Accident
DBC	Diagnose Behandel Combinatie
EEG	Electro-encephalogram
EMV	Eye opening-best Motor response-Verbal respons (Glascow Coma Scale)
EPC	Epilepsia Partialis Continua
EPSE	Elementary Partial Status Epilepticus (= SPSE)
ESES	Electrical Status Epilepticus during Slow Sleep
GABA	Gamma-Amino-Butyric-acid
GCSE	Generalized Convulsive Status Epilepticus
i.m.	intra-muscular
i.v.	intra-venous
ICP	Intracranial pressure
ICU	Intensive Care Unit
LKS	Landau-Kleffner Syndrome
MR	Mental retardation
MRI	Magnetic Resonance Imaging
NCSE	Nonconvulsive Status Epilepticus
No-SE	Wrong diagnosis of Status epilepticus
NSE	Neuron specific enolase
NMDA	N-Methyl-D-Aspartate
PHT	Phenytoin
SD	Standard Deviation
SE	Status Epilepticus
SIG	Stichting Informatiecentrum Gezondheidzorg (Bureau of Healthcare Information)
SPSE	Simple Partial Status Epilepticus (= EPSE)
TCSE	Tonic-Clonic Status Epilepticus
VG	Verstandelijk Gehandicapten

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